UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
4330 EAST WEST HIGHWAY
BETHESDA, MARYLAND 20814

Memorandum

Date: JAN 2 2 2009

TO : Office of the General Counsel
Office of Hazard Identification and Reduction

FROM : Todd A. Stevenson, Director,
Office of the Secretary

SUBJECT : Prohibition on the Sale of Certain Products Containing Specified Phthalates
Section 108 of the Consumer Product Safety Improvement Act (CPSIA)
Comments due – January 12, 2009

COMMENT	DATE	SIGNED BY	AFFILIATION
1	11/17/08	Sonya M. Kiehna Environmental and Safety Manager	Schutt Sports 1200 Union Avenue Litchfield, IL 62056
2	11/17/08	Jack Summersell President	Educators Resource 2575 Schillinger Rd. N. Semmes, AL 36575
3	11/18/08	M.P. Catan Product Compliance	Darice Inc./Lamrite West 13000 Darice Pkwy. Strongsville, OH 44149
4	11/19/08	Val Dingman	vdingman@trevcoinc.com
5	11/19/08	Christopher Hudgins, VP Government Relations & Policy	International Sleep Products Association (ISPA) 501 Wythe Street Alexandria, VA 22314
6	11/21/08	Joel Wilson Senior Design Engineer	Burley Design joel@burley.com
7	11/26/08	John W. Frisch	johnfrisch@verizon.net

COMMENT	DATE	SIGNED BY	AFFILIATION
8	11/27/08	Mark Sassak President	Saturnian 1 Inc. PO Box 700538 Plymouth, MI 48170
9	12/01/08	anonymous	
10	12/03/08	Timothy E. Sullivan Deputy Attorney General Edward G. Weil Sup. Deputy Attorney General	Edmund G. Brown Jr. Attorney General Department of Justice 1515 Clay Street, 20th FL Oakland, CA 94612
11	12/04/08	Stephanie Lester VP, International Trade	Retail Industry Leaders Association 1700 N Moore St. Ste 2250 Arlington, VA 22209
12	12/05/08	Alan R. Klestadt Tracey Topper-Gonzalez	Grunfeld, Desiderio, Lebowitz, Silverman & Klestadt LLP Counselors at Law 399 Park Avenue 25th Floor New York, NY 10022-4877
13	12/08/08	Carol Pollack-Nelson, Ph.D. Independent Safety Consulting	13713 Valley Drive Rockville, MD 20850-5402
14	12/16/08	Matt Cantor	Cantor Inspections 1105 High Ct. Berkeley, CA
15	12/18/08	Cassandra Carmichael Director, Eco-Justice Program	National Council of the Churches of Christ in the USA
16	12/21/08	Candace Allgood	jscsmjra@yahoo.com

COMMENT	DATE	SIGNED BY	AFFILIATION
17	12/23/08	Chuck Satterlee Director of Operations	Allentown Toy Manuf. Co. 725 N. 10th Street Allentown, PA 18102
18	1/05/07	Nermine Hassan	nermine@occupant.org
19	1/06/09	Melody A. Sharpnack	melody@burch@msn.com
20	1/07/09	Virginia L. Tippey Compliance Officer	Organic Mattresses, Inc. PO Box 2094 Grass Valley, CA 95945
21	1/07/09	Paul Thomsen Business Dev. Manager	Matta Products Limited 6 Canon Place, Pakuranga PO Box 251285 Auckland 2140, New Zealand
22	1/07/09	Rachel Weintraub Director, Product Safety & Senior Counsel	Consumer Federation of America
		Janell Duncan Senior Counsel	Consumers Union
		Donald Mays Senior Director, Product Safety and Technical Public Policy	Consumers Union
		Ami Gadhia Policy Counsel	Consumers Union
		Ed Miezwinski Consumer Program Director	U.S. Public Interest Group
		Elizabeth Hitchcock Public Health Advocate	U.S. Public Interest Group

COMMENT	DATE	SIGNED BY	AFFILIATION
22 cont'd.	1/07/09	Nancy A. Cowles Executive Director	Kids in Danger
		Celia Wexler Washington Representative Scientific Integrity Program	Union of Concerned Scientists
		Diana Zuckerman President	National Research Center for Women & Families
		David Arkush Director, Congress Watch	Public Citizen
23	1/07/09	LaVonne Fishell	lfishell@cfl.rr.com 4047 Teriwood Avenue Orlando, FL 32812
24	1/07/09	Ann Simon	dik3ann@tds.net
25	1/08/09	Jim Coleman Quality & Compliance Manager	Ball Bounce & Sport, Inc., Hedstrom 1401 Jacobson Avenue Ashland, OH 44805
26	1/08/09	Teresa N. Quarles	tnq113@aol.com Augusta, GA
27	1/08/09	Tim Zacharewski, Ph.D.	Michigan State University Dept. of Biochemistry & Molecular Biology 501 Biochemistry Bldg. Wilson Road East Lansing, MI 48824-1319
28	1/08/09	Christy Nyboer Owner & Designer	Little Lark christy@alittlelark.com
29	1/09/09	Erica Hamblen	Erica_hamblen@yahoo.com

COMMENT	DATE	SIGNED BY	AFFILIATION
30	1/09/09 & 1/12/09	J Patrick Harmon, Ph.D. Industry Manager Oxo Alcohols And Plasticizers	BASF Corporation 1111 Bagby Street Houston, TX 77002
31	1/09/09	Richard Labov Chairman	Union Ink Company, Inc. 453 Broad Avenue Ridgefield, NJ 07657
32	1/09/09	Jim Cronin Product Ecology Manager	EMT, Inc. jcronin@emt.com
33	1/10/09	Christine D. Richard	Books From the Bayou canefarm@charter.net
34	1/12/09	James D. Isner Vice President	Polymer Diagnostics Inc. 33587 Walker Road Avon Lake, OH 44012
		David A. Ernes, Ph.D.	Polymer Diagnostics Inc. ernesd@polymerdiagnostics.com
35	1/12/09	Carter Keithley President	Toy Industry Association 115 Broadway, Suite 400 New York, NY 10010
36	1/12/09	Bruce E. Richter, Ph.D. Manager Richard Carlson, Ph.D. Staff Chemist ASTM D20.70 Subcommittee Chairman ASTM F40.01 Vice Chair Sheldon Henderson, MBA Product Manager Eric Francis, Ph.D. Staff Chemist	Dionex Corporation Dionex Salt Lake City Technical Center 1182 W. 2400 S. Ste. A Salt Lake City, UT 84119

COMMENT	DATE	SIGNED BY	AFFILIATION
37	1/12/09	Marcia Y. Kinter VP – Government and Business Information	Specialty Graphic Imaging Association 10015 Main Street Fairfax, VA 22031
38	1/12/09	William L. Kovacs Vice President Environment, Technology & Regulatory Affairs	Chamber of Commerce of the United States of America 1615 H Street, NW Washington, DC 20062
39	1/12/09	Allen Blakey VP – Industry & Govt. Affairs	The Vinyl Institute 1300 Wilson Blvd. Arlington, VA 22209
40	1/12/09	Worth Jennings Global Oxo Marketing	ExxonMobil Worth.a.Jennings@exxonMobil.com
41(a)	1/12/09	Kristy L. Morrison Manager, Chemical Products & Technology Division (Phthalate Esters Panel)	American Chemistry Council 1300 Wilson Boulevard Arlington, VA 22209
41(b)	1/12/09	Kristy L. Morrison Manager, Chemical Products & Technology Division (Non Phthalate Ester Plasticizers Panel)	American Chemistry Council 1300 Wilson Boulevard Arlington, VA 22209
42	1/12/09	Janet Nudelman Director of Program & Policy	Breast Cancer Fund
		Rachel Weintraub Director of Product Safety and Senior Counsel	Consumer Federation of America
		Donald L. Mays Senior Director of Product Safety and Senior Counsel	Consumer Union

COMMENT	DATE	SIGNED BY	AFFILIATION
42 cont'd.	1/12/09	Nancy A. Cowles Executive Director	Kids in Danger
		Diana Zuckerman President	National Research Center for Women & Families
		David Arkush Director, Congress Watch	Public Citizen
		Ed Mierzwinski Federal Consumer Program Director	U.S. Public Interest Group
		Elizabeth Hitchcock Public Health Advocate	U.S. Public Interest Group
43	1/12/09	Bill Sells Vice President Government Relations	Sporting Goods Manufacturers Association BSells@sgma.com
44	1/12/09	Sarah Janssen, MD, PhD, MPH Staff Scientist	Natural Resources Defense Council 111 Sutter St., 20th Floor San Francisco, CA 94104
45	1/12/09	Kevin M. Burke President and CEO	American Apparel & Footwear Association 1601 North Kent Street Suite 1200 Arlington, VA 22209
46	1/13/09	Robert Waller, Jr., CAE President	Juvenile Products Manufacturers Association 15000 Commerce Parkway Suite C Mt. Laurel, NJ 08054
47	1/14/09	Linda Hays	Hopscotchtoys McMinnville, OR

COMMENT	DATE	SIGNED BY	AFFILIATION
48	1/14/09	Kevin Madigan, President & Ian MacDonald, VP & General Manager	Century Novelty 382 Plymouth Road Livonia, MI 48150
49	1/14/09	Ric Dilz President	Rein Designs, Inc. 2400 Central Ave. Suite C Boulder, CO 80301
50	9/30/08	Lawrence Chan Chairman	Hong Kong Toy Council Tsimshatsui, Kowloon, Hong Kong
51	1/19/09	Scott Silverstein Chief Executive Officer	Nina Footwear Corp. 200 Park Ave South New York, NY 10003
52	1/12/09	Robert Johnson President	Child Safety Task Force
53	1/20/09	Robb Ruyle President	Powderhorn Industries, Inc. 931 N. Park Avenue Montrose, CO 81402

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November 17, 2008

Cheryl Falvey
CPSC General Council

Re: Consumer Product Safety Improvement Act of 2008 Title I: Sec. 108.

Dear Ms. Falvey:

This will serve as our formal legal opinion concerning issues which have been raised with the implementation of the Consumer Product Safety Improvement Act (CPSIA) of 2008. Specifically, Title I: Sec. 108 of HR 4040 relates to Children's Product Safety and more specifically to children's" toys" containing phthalates. This Act, in part, requires a General Certificate of Conformity and includes a prohibition of sale of certain products containing specified phthalates

Summary of Relevant Legislation

Children's Toys are defined in the legislation as "a consumer product designed or intended by the manufacturer for a child 12 years of age or younger for use by the child when the child plays". The legislation asserts that there is scientific evidence that phthalates have adverse affects on humans, an argument that is contrary to the position of the American Chemistry Counsel.

We note that the Act is remarkably broad in that there is virtually no limitation as to the definition of "toy" other than anything that a child uses when playing. However, notwithstanding nor disregarding this broad language, it is our opinion as follows:

First, our products under consideration, namely football, baseball/softball helmets and other protective equipment are intended (and often required) to be worn by children and young men or women while participating in sports. These protective products are not covered by the Act notwithstanding its broad language.

1200 E. UNION AVENUE · LITCHFIELD, ILLINOIS 62056 · USA · (217) 324-2712 · FAX (217) 324-2855 · www.schuttsports.com

A football, baseball or softball helmet is a protective **device**. Although it is worn whilst "playing" football, softball or baseball, the product is not in and of itself a toy. It is a protective device designed, manufactured and distributed as such. It must meet certain mandated criteria as protective equipment and satisfy nationally-adopted impact standards in order to comply with the requirements of the sport of football, baseball/softball etc. for protection while participating in competition, or practice.

Second, football, baseball/softball helmets and other protective equipment are mandated by the rules of governing bodies to be worn at virtually every formal level of play from four (4) or five (5) years of age on up. While a toy is something the child plays directly with, the football, baseball or softball helmet is one of several protective devices worn by one participating or competing in that sport. The same could be said for the athletic supporter, the plastic cup, or the face shield. Even a baseball hat worn during a baseball game is not considered a toy.

Third, football, baseball and softball helmets are required in organized sports at any age and must be worn by all who participate as an article of protective equipment. Even younger children often wear football, baseball/softball helmets and other protective equipment at the behest of their parents for protection when "playing" ball. The definition of "toy" and "protective device" are mutually exclusive in this statutory context.

Last, our "Collectible" miniature helmets are not toys. They cannot be worn and are not intended for use, or "to play with" but encased for purchase and display or support of one's team. Further, your customers do not perceive your collectibles as "toys", but rather as a piece of memorabilia having potential value after purchase.

You may anticipate challenges to this legislation from various industries, but we do not find any relevance or compliance requirements on the part of Schutt as to this legislation for your lines of protective equipment.

If you would have any further questions or require a more substantive analysis of the Act, its definitions and/or provisions beyond our initial review and evaluation of the material, please advise. I would appreciate it if you will contact me in any event upon your receipt of this letter to confirm your receipt of same.

Very truly yours,

Sonya M. Kieh

Sonya M. Kiehna
Environmental and Safety Manager
Schutt Sports

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Stevenson, Todd

From: Jack Summersell [jack.summersell@edresource.com]
Sent: Monday, November 17, 2008 3:22 PM
To: Phthalates Project
Subject: Comments on CPSIA Section 108 - Phthalates

Categories: Question

Dear Commission,

Please clarify whether Section 108 applies retroactively to existing inventories.

Also, with specific regard to the retroactive treatment of existing inventories, please note that wholesalers, retailers and distributors have so many different products from so many different manufacturers, and so few of each item, that it is not financially feasible for most wholesalers, retailers and distributors to conduct our own testing. Furthermore, in many cases, retailers and distributors are not in possession of sufficient quantities to conduct proper testing. We are thus completely dependent on manufacturers to conduct their testing and to provide results to us regarding phthalates levels in a timely fashion.

Based on response rates from manufacturers to date, it is almost certain that wholesalers, retailers and distributors will not know, by Feb 10, 2009, which of the items in our inventories contain phthalates in excess of the new limits. In fact, my company is predicting that, despite our intense efforts to obtain this information from our manufacturers, strict compliance with any "retroactive treatment of inventory" aspect of this law would be achieved only through massive inventory write-downs, quite possibly resulting in business failure.

Finally, please note that the period of time between the effective date of the Act and Feb 10, 2009 might be sufficient for manufacturers to sell through existing inventories. However, it will take many months for the typical product to make its way out of the supply chain. Thus, the fact that manufacturers, wholesalers and retailers are required to have emptied the newly designated hazardous products from their shelves all on the same day is fundamentally unfair to wholesalers and retailers. If the manufacturers can sell to wholesalers, distributors and retailers "above the limits" up through Feb 9, 2009, then wholesalers, retailers and distributors should be given time to resell the merchandise.

Our desire and intent is to comply with the new law. We support the intent and spirit of the end result of the law, improving children's safety. But retroactive treatment of existing inventory and the concurrent deadline for all types of business presents scenarios that might result in a choice between non-compliance and business failure.

Again, please clarify whether Section 108 applies retroactively to existing inventories for phthalates.

Thank you for your consideration of my comments.

Regards,

Jack Summersell
President
Educators Resource

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jack.summersell@edresource.com
www.ERdealer.com

EDUCATORS RESOURCE

2575 Schillinger Rd N · Semmes, AL 36575

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Stevenson, Todd

From: Catan, MP [MPCatan@Darice.com]
Sent: Tuesday, November 18, 2008 3:38 PM
To: Phthalates Project

Categories: Comment

Regarding the phthalates requirement, from what I have read there is currently is no exception for inaccessible parts as there is with lead. I think this is unnecessary and the rule should be changed to only accessible parts, or parts that are exposed only after use and abuse testing. Thank you.

M.P. Catan
Product Compliance
Darice Inc./Lamrite West
13000 Darice Pkwy.
Strongsville, OH. 44149
PH: 440-878-3550
Fax: 440-846-0991

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Stevenson, Todd

From: Val Dingman [vdingman@trevcoinc.com]
Sent: Wednesday, November 19, 2008 9:23 AM
To: Phthalates Project
Subject: Children's Apparel

Categories: Comment

Concerning phthalates:
There really is no clear cut direction on children's apparel. By the CPSIA descriptions, it does not fall into the "toy" category and it does not fall into the "child care product" category. It would seem that it would be considered a children's product but there is no direction or timeline for a "children's product." There needs to be more clarification for this entire category of product.

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ISPA

INTERNATIONAL
SLEEP
PRODUCTS
ASSOCIATION

November 19, 2008

Consumer Product Safety Commission
Office of the Secretary
Room 502
4330 East West Highway
Bethesda, Maryland, 20814

The International Sleep Products Association (ISPA) submits the following comments to the Consumer Product Safety Commission (CPSC) on behalf of the mattress manufacturing industry regarding the interpretation of the term "child care article" as defined by Section 108(e)(1)(C) of the Consumer Product Safety Improvement Act (CPSIA), in support of our position that the CPSC conclude that a mattress does not fall within the scope of this term.

Section 108(e)(1)(C) defines a "child care article" as "a consumer product designed or intended by the manufacturer to facilitate sleep or the feeding of children age 3 and younger."

ISPA urges the CPSC to conclude that a mattress is not subject to this definition. As a matter of statutory construction, we note that at numerous points in the CPSIA, when Congress intended to focus on specific categories of products on which children sleep, it did so by specifically naming those products. Examples include CPSIA Sections 102(a)(3) (cribs), 104 (c) (cribs), 104(f) (cribs), and 107(B) (cribs and mattresses). By contrast, in defining "child care article" in Section 108(e)(1)(C), Congress made no specific references to these types of products.

Looking at the definition from a functional perspective, a mattress is a passive, non-mechanical, non-motorized product that is designed and intended to be used for sleeping or resting. Other products are intended to "facilitate" a person's ability to fall asleep or to rest, so that he or she may then sleep or rest on a mattress or other surface. In the case of children under the age of 3, those other products might include a rocker, swing, music player, and other non-mattress product that actively helps soothe, calm and relax the child so that he or she can achieve sleep or rest.

For these reasons, we urge the Commission to interpret the term "child care article" to exclude mattresses.

Sincerely,

Christopher Hudgins
Vice President, Government Relations & Policy

501 Wythe Street ■ Alexandria, Virginia 22314-1917 ■ (703) 683-8371 ■ Fax (703) 683-4503
www.sleepproducts.org ■ info@sleepproducts.org

Stevenson, Todd

From: Chris Hudgins [CHudgins@sleepproducts.org]
Sent: Wednesday, November 19, 2008 11:48 AM
To: Phthalates Project; CPSC-OS
Subject: ISPA Comments on Child Care Articles/Phthalates
Attachments: ISPA Comments on child care articles phthalates.pdf

Please see attached comments from ISPA regarding the definition of a "child care article."

Chris Hudgins
Vice President, Government Relations & Policy
International Sleep Products Association
501 Wythe Street
Alexandria, VA 22314
Ph: (703) 683-8371 x1113
Fax: (703) 683-4503
www.sleepproducts.org
"Start Every Day With a Good Night's Sleep ™"

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Stevenson, Todd

From: Joel Wilson [joel@burley.com]
Sent: Friday, November 21, 2008 6:19 PM
To: Phthalates Project
Cc: Comcast Michael Coughlin; Wagner, Brad; Troy Cameron; Val Hoyle

To Whom It May Concern:

I am writing in response to the request for information regarding phthalates (108rfc). Burley Design makes child products that are neither toys or child care articles by the definitions listed in CPSIA Section 108(e)(1)(B&C). While the CPSIA phthalate ban does not directly apply to our products we are staying abreast of developments in the industry in the pursuit of continuous improvement.

The third bullet on page two of the request for comments document asks "What children's products other than toys, toys that can be mouthed, or child care articles contain PVC or vinyl plastic, and why?"

Our child carrying bicycle trailers contain PVC windows which have DEHP as the plasticizer. These trailers are outdoor products which must withstand hot and cold temperatures while maintaining flexibility, and they must not degrade under UV radiation from sunlight.

We have been researching and testing alternatives to window materials that contain DEHP, BBP and DBP for over a year. While there are basic alternatives available, there are none in the market that withstand the environmental conditions required for our product.

We have tested many samples of different TPU, TPE, and phthalate free PVC from multiple vendors. Our testing has included tensile testing, cold temperature durability and UV exposure. All TPU samples turn yellow within a few days of normal outdoor exposure to sunlight. This is an aesthetic issue which our customers do not find acceptable. The TPE samples were not durable enough and the phthalate free PVC samples became very brittle and crack in cold temperatures which would expose the child to cold, rain and wind.

To our knowledge there is no other manufacturer of similar child products that are also outdoor products that has successfully implemented an alternate material to PVC window materials that contain phthalates.

Best regards,

Joel Wilson
BURLEY DESIGN
Senior Design Engineer
direct 541.868-3140
fax 541.687.0436
skype burley-joel
www.burley.com

Stevenson, Todd

From: Information Center
Sent: Wednesday, November 26, 2008 10:44 AM
To: 'johnfrisch@verizon.net'
Subject: RE: Message from Email Form

Hello,

We have forwarded your inquiry over to the Office of the Secretary (OS) within the CPSC, where they will be noted and added to any other comments that we receive.

Thank you,

mlj

From: emailform@cpsc.gov [mailto:emailform@cpsc.gov]
Sent: Tuesday, November 25, 2008 5:28 PM
To: Information Center
Subject: Message from Email Form

11/25/2008 17:27:03

Name = John W. Frisch
Organization/Affiliation = John W. Frisch, P.E.
Daytime Phone = 908-526-0082
E-mail address = johnfrisch@verizon.net

Message = Dear Chairman Nord, Please enforce the Consumer Product Safety Improvement Act and make sure toys with over-the-limit levels of phthalates are off store shelves by February, 2009. Protect Kids, not chemical companies. I strongly feel that the manufactures/distributors/retailers of products containing phthalates can easily survive the possible financial loses involved with scrapping these products rather than continuing to allow them to be sold. I can't put a dollar value on the health and safety of even one child, but I know it is more than the loss these companies could incur. Sincerely,

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Stevenson, Todd

From: SAT1SPORT@aol.com
Sent: Monday, December 01, 2008 3:18 PM
To: Phthalates Project
Subject: CPSIA of 2008, Section 108, Phthalates

Categories: Comment

November 27, 2008

Dear CPSC,

We are writing to express our concerns about the new CPSIA of 2008, Section 108 **Phthalate ban** and its effects on our small business.

We are a small business in Michigan that imports and distributes our own unique, patented brand of sport related products. We have been in business for 20 years starting in our basement with one product and now have over eighty items. As an inventor I hold ten U.S. Patents on assorted Sport related products and materials, which are currently used and marketed on our footballs, soccer balls, volleyballs and other assorted games and sport items. Our product is known in the market place for its safety, durability and our unique patented gripping materials. We have a customer base that includes ages from elementary, high school, college, as well as adults. PE teachers across the country use our products as safe, soft, non-threatening training products for both young and old.

Our products build confidence when learning to play a sport and encourage being active, exercise and safe play.

Our web site is www.sat1sport.com.

In reference to Section 108 of the CPSIA limits on the amounts of certain types of **phthalates** in certain specific categories of children's products to be banned within 180 days after enactment.

These standards and time frames as they stand will jeopardize our company for the following reasons:

<u>Time Frames:</u>

Phthalates have been in the market place for over 50 years in products to numerous to list. To deplete existing inventories for manufacturers, wholesalers, distributors and retailers **in 180 days**

Is impossible and unachievable without causing financial hardships and demise for many companies.

<u>Testing:</u>

Our product has always been in compliance with ASTM F963 standards for Mechanical, Hazard, Flammability and Lead Content, **but we were never required to test for phthalates even for EN71 testing.**

To test our current inventory for phthalates would cost over $100,000 and we cannot financially afford to do this testing or supply certification for our existing inventory. This does not include the costs for technical and legal advise to evaluate our product.

In the past twenty years we have not had one report of injury or harm from use of our products nor have we had one recall.

Inventories:

Our material suppliers and factory have worked diligently to comply with the new phthalate standards for new product manufactured as of November 12, 2008 and all of our new inventory imported will be in compliance accompanied with General Certificates of Conformity.

The problem is our existing inventory in stock manufactured prior to the effective date of the CPSIA. Our current inventory is an 18–24 month supply in a good market. We do not sell to mass retailers i.e. Wal-Mart or Kmart so our inventory doesn't turn as quickly as some of the larger suppliers. Due to the poor economic conditions and a 30% decrease in 4th quarter sales, it may take even longer to sell through. Our customer base varies from mom-n-pop stores, specialty stores, college bookstores, independent sporting goods stores and school suppliers. Some of our smaller retailers can have inventory for 2-5 years.

We need to be given enough time to sell and deplete existing inventory to retailers and customers allowing a smooth transition into new inventory purchases. We cannot afford to just discard our current inventory and finance purchasing new inventory. This would be a significant financial hardship for us, forcing us out of business and filing bankruptcy.

Certification:

There are different interpretations and confusion concerning the **phthalates ban** and **inventories**. The testing labs and legal advisors cannot give us clear answers or direction on many issues because they are still unresolved. We are still uncertain as to how the new laws apply to sporting good products and if our products fall under the new restrictions.

We have retailers demanding effective immediately any product shipped as of now is phthalate free and certificates must be supplied because of the February 10, 2009 deadline. This has caused panic with both retailers and consumers.

The deadline pertaining to phthalates needs to be reconsidered because we have customers canceling orders, refusing to accept current inventory, demanding certificates we can't supply on existing inventory, removing inventory from their shelves and holding payment on invoices.

We are unable to get more credit to purchase new inventories in this economic credit crisis. Our home is on the line as collateral for our current credit. We will be out of business by January if we cannot sell our current inventories. If the retailers start removing product from their shelves that they feel does not comply for use of children twelve years and under it will be an economic disaster for suppliers and retailers. We don't need more companies going out of business and filing bankruptcy in this current economic crisis.

I can understand possible harm for a three year old or younger chewing or sucking on a product containing phthalates, i.e. a baby bottle, pacifier, teething ring or any object under 1.75 inches. This seemed to be the initial intent of the phthalate ban. We feel our products fall in the sporting goods, fitness and licensed products category. To determine whether a football is a toy or sport product should be analyzed by how it is made and used. As an example, our footballs are manufactured to official sizes and weights; Inflatable Butyl bladders are used for long lasting retention. They are constructed with hand-sewn lacing that provides finger and hand control when throwing and catching and are used in the game of football or recreation. The same goes for our soccer balls, volleyballs or basketballs. It is confusing to determine if this is a product that can be chewed, sucked or licked when the average diameter is 6 inches and larger. Times have changed where PE and recreational departments are teaching the fundamentals of sports to children from the age of three years and up. They are taught to play flag football, soccer, golf and other sports under adult supervision and it is highly unlikely a child would chew, lick or suck on one of these sport products.

It seems to me a child is more susceptible to harm from the bacteria, germs and viruses from the environment they play in and from what the product makes contact with, i.e. animal saliva, feces, toxic ground chemicals, dirt, mud, their own runny noses and dirty hands then licking or chewing on a sport product. In short the environment that the football is played in seems more dangerous and toxic than the small amount of phlatates that could be found in PVC materials.

There are millions of yards of PVC shelf liners, bathtub liners, baby mats, non-slip rug liners, etc. that are used in concealed spaces in over 50 millions homes to store our silverware, glasses, utensils and food products, which are then placed in our mouths daily. Wal-Mart, Kmart, Sears and all the major retailers sell millions of yards of these products that contain PVC and phthalates.

I feel this is more hazardous and toxic than a sport product not meant to be put in your mouth or licked.

The bottom line is we all want a safer world clean of toxins. Realistically for our small sport supply company to completely comply with the phthalate standards in PVC sport related products, we need a minimum of 3-5 years to be in full compliance and be able to deplete present inventory.

We are pleading with the CPSC to enact a reasonable time frame for depleting suppliers existing inventories and retailers existing shelf inventory and issue a clear and concise statement reassuring suppliers, retailers and consumers that existing inventory manufactured prior to the CPSIA is acceptable to sell or purchase without certification or penalty concerning phthalates after February 10,2009.

We respectfully ask for an urgent response to clarify our concerns and allow us either an exemption, extension and clarify if our sport products are subject to the ban. This is already causing our company a financial hardship. It is critical for the survival of our company.

We truly appreciate the CPSC's time and consideration to review our comments and concerns related to the CPSIA.

Respectfully,

Mark Sassak, President

Saturnian 1 Inc.

PO Box 700538

Plymouth, MI 48170

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F: 734-454-6514

Sat1sport@aol.com

www.sat1sport.com

Stevenson, Todd

From: Babich, Michael
Sent: Monday, December 01, 2008 10:46 AM
To: Phthalates Project
Subject: FW: Message from Email Form

Categories: Legal comment

Mike Babich
Health Sciences
301-504-7253
mbabich@cpsc.gov

From: Stevenson, Todd
Sent: Monday, December 01, 2008 8:40 AM
To: DiMatteo, David; Babich, Michael
Subject: FW: Message from Email Form

Todd Stevenson
Director, Office of the Secretary
Division of Information Management
Office of Information and Technology Services
US Consumer Product Safety Commission
(301) 504-6836, Fax (301) 504-0127

From: Information Center
Sent: Friday, November 28, 2008 9:38 AM
To: Stevenson, Todd
Cc: Wolfson, Scott; Fleming, Nychelle
Subject: FW: Message from Email Form

Todd,

Please note these as comments even though the consumer did not leave any of her contact information.

Thank you,

Michael June

From: emailform@cpsc.gov [mailto:emailform@cpsc.gov]
Sent: Wednesday, November 26, 2008 8:28 PM
To: Information Center
Subject: Message from Email Form

11/26/2008 20:27:18

Name =

Organization/Affiliation =
Daytime Phone =
E-mail address =

Message = I am contacting CPSC to tell you that toys with over-the-limit levels of phthalaes need to come off the shelves by February 2009, as the law states. Toxic phthalates need to be removed from the market for the health and safety of our children and grandchildren. In my opinion removal of these toxins should be immediate and not wait until Feb. 2009. Thank you in advance for immeiately attending to this matter.

EDMUND G. BROWN JR.
Attorney General

State of California
DEPARTMENT OF JUSTICE

1515 CLAY STREET, 20TH FLOOR
P.O. BOX 70550
OAKLAND, CA 94612-0550

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Facsimile: (510) 622-2270
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December 3, 2008

VIA E-MAIL & FIRST CLASS MAIL
cfalvey@cpsc.gov

Cheryl A. Falvey, Esq.
General Counsel
Office of the General Counsel
U.S. Consumer Product Safety Commission
4330 East West Highway
Bethesda, MD 20814

RE: Implementation of California State Law Restricting Phthalates

Dear Ms. Falvey:

In light of the recent public debate concerning the applicability of the federal phthalate restrictions in the Consumer Product Safety Improvement Act of 2008 ("CPSIA"), we are writing to explain our position on the applicability of California's phthalate limits on toys and child care articles. In short, California's phthalate restrictions become effective January 1, 2009, and prohibit the manufacture, sale, or distribution of toys and child care articles with excessive levels of certain phthalates, regardless of when or where those items were manufactured.

Your letter of November 17, 2008, stated that the federal phthalate restrictions in section 108 of the new CPSIA apply only to products manufactured after that provision's effective date of February 10, 2009. Under this interpretation of the federal law, manufacturers can continue making toys with significant amounts of phthalates, and sell them in this country for years to come, so long as they were made by February 9, 2009. In response to your letter, members of Congress have sent letters to CPSC objecting to this interpretation and explaining that Congress intended that children's toys and child care articles with excessive level of phthalates cannot be sold after February 10, 2009, even if they were manufactured earlier.

Regardless of which of these interpretations of the federal CPSIA prevails, toys and child care articles containing excessive levels of phthalates cannot be sold or distributed in California after January 1, 2009, no matter when or where they were manufactured. This California requirement is not preempted or otherwise affected by the federal CPSIA phthalate restrictions. While it is not CPSC's obligation to advise companies on the applicability of state law, we are concerned that since your November 17, 2008, letter does not mention the existence of state phthalate requirements, readers could mistakenly conclude that there will be no phthalate limitations in effect anywhere in the United States on January 1, 2009. We hope that this letter will provide guidance to the public as to how the federal and state phthalate laws interact.

California's phthalate restrictions

In October of 2007, Governor Schwarzenegger signed Assembly Bill 1108 ("A.B. 1108"), which limits the phthalate content of toys and child care articles[1] manufactured, distributed, or sold in California. (Cal. Health & Saf. Code, §§ 108935-108939, Stats. 2007, c. 672, A.B. 1108.) This California law restricts six particular phthalates, which are the same as those restricted by the federal CPSIA: di-(2-ethylhexyl) phthalate ("DEHP"), dibutyl phthalate ("DBP"), benzyl butyl phthalate ("BBP"), diisononyl phthalate ("DINP"), diisodecyl phthalate ("DIDP"), and di-n-octyl phthalate ("DnOP"). Three of the phthalates, DEHP, DBP and BBP ("Group 1"), may not be present in concentrations exceeding 0.1 percent in any toy or child care article. The remaining three phthalates, DINP, DIDP, and DnOP ("Group 2"), are restricted to 0.1 percent only in those toys and child care articles "intended for use by a child under three years of age if that product can be placed in the child's mouth." (Cal. Health & Saf. Code, § 108937, subd. (b).)

A.B. 1108's restrictions take effect January 1, 2009. On that date, "no person or entity shall manufacture, sell, or distribute in commerce" any of the toys or child care articles violating its provisions. (Cal. Health & Saf. Code, § 108937, subd. (a), (b).) Thus, even if a product was manufactured before January 1, 2009, it cannot be sold in California by a retailer after that date unless it meets the A.B. 1108 phthalate standards.

A violation of A.B. 1108's phthalate standards is an unlawful act in violation of California's Unfair Competition Law.[2] (Cal. Bus. & Prof. Code, § 17200, et seq.) Violations of the Unfair Competition Law may be enforced through a civil action brought by the Attorney General or a district attorney in the name of the People, by certain city attorneys, and by individual persons who have "suffered injury in fact and lost money or property" as a result of the violation. (Cal. Bus. & Prof. Code, § 17204.)

In addition, while manufacturers and distributors have no express duty under A.B. 1108 to stop distributing and manufacturing products that do not comply with A.B. 1108 before January 1, 2009, sale of a non-compliant product at a time and place that makes it likely that the product will be offered for sale after January 1, 2009, could violate other legal duties. It may violate warranties or other contractual agreements among the parties in the chain of distribution,

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[1] A "toy" is defined as a "products designed or intended by the manufacturer to be used by children when they play." (Cal. Health & Saf. Code, § 108935, subd. (a).) A "child care article" is defined as "all products designed or intended by the manufacturer to facilitate sleep, relaxation, or the feeding of children, or to help children with sucking or teething." (Cal. Health & Saf. Code, § 108935, subd. (b).)

[2] A.B. 1108 does not contain any provision authorizing any agency to adopt implementing regulations or guidelines, nor does it contain any enforcement provisions itself.

or it may create a threatened violation of A.B. 1108, which the Attorney General can seek to enjoin under the Unfair Competition Law. Thus, distributors and manufacturers should assess their chain of distribution and take action to assure that these issues do not arise.

Finally, even before January 1, 2009, it is illegal in California to expose persons to certain phthalates without providing a clear and reasonable warning. (Cal. Health & Saf. Code, §§ 25249.5-25249.13 [commonly known as "Proposition 65"].) As discussed further below, this requirement has been in effect and will continue to be in effect after January 1, 2009.

No federal preemption of California's phthalate restrictions

California's A.B. 1108 phthalate restrictions are not preempted by the new federal CPSIA. To the extent that federal and California phthalate restrictions overlap, they are identical. To the extent that there are any products that are subject to A.B. 1108's phthalate standards for which there are no federal phthalate requirements at all, there is no federal requirement that could preempt state law. CPSIA, therefore, does not preempt California's phthalate restrictions.

Section 108 (d) of CPSIA provides that the standards for phthalates are "consumer product safety standards," which apparently means that they have the preemptive effect given by section 26(a) of the Consumer Product Safety Act. (15 U.S.C. § 2075(a).) That section states that a federal consumer product safety standard preempts a state law that — as to a risk of injury associated with a given consumer product — "prescribes any requirements as to the performance, composition, contents design, finish, construction, packaging or labeling of such product," "unless such requirements are identical to the requirements of the Federal standard." (*Id.*)

Even if A.B. 1108's phthalate restrictions are considered to be requirements on "composition" or "contents" of a product, A.B. 1108 is not preempted because its restrictions on the phthalate content of a given consumer product are identical to any applicable federal restriction. Indeed, CPSIA adopted the same phthalate restrictions that had previously been enacted in A.B. 1108. CPSIA sets the same concentration limit (0.1 percent) on the same six phthalates as does A.B. 1108, and both statutes use the same Group 1/Group 2 approach to the types of products covered by their standards. A product that is subject to and complies with CPSIA's phthalate limits would also comply with A.B. 1108's phthalate limits, and vice versa. As to all products that fall under the scope of both statutes, A.B. 1108 and CPSIA apply the same percentage content restrictions to the same phthalates. Because state and federal law are identical in this respect, the state law is not preempted. (15 U.S.C. § 2075(a).)

To the extent that A.B. 1108 may apply its standards to a broader category of products than does CPSIA, those additional products are not subject to a federal standard at all, and therefore there is no preemption. For instance, A.B. 1108 defines child care articles to include things that facilitate "sleep, relaxation, or the feeding of children," while CPSIA omits the term "relaxation." CPSIA limits child care articles to those intended for children age three or younger, while A.B. 1108 contains no age limitation. CPSIA defines toys as products intended for play by children "12 years of age or younger," while A.B. 1108 contains no age limitation on "children." CPSIA has a specific definition of what "can be placed in a child's mouth," while A.B. 1108 does not. Importantly, A.B. 1108 does not apply different requirements to the products covered by CPSIA, it simply applies the identical standard to a somewhat broader class of products. In other words, there may be some products to which CPSIA provides no phthalate limits at all that would be subject to regulation under A.B. 1108.

Furthermore, during the time in which there is no federal phthalate consumer product safety standard in effect as to a product, there is no preemption. Section 26(a) of the Consumer Product Safety Act preempts a non-identical state requirement on a product only during the time when "a consumer product safety standard . . . is in effect and applies to a risk of injury associated with a product." (15 U.S.C. § 2075(a).) Prior to February 10, 2009, there is no federal consumer product safety standard in effect at all with respect to phthalates in toys and child care articles, so there can be no preemption prior to that date under any circumstance.

In addition, if the position in your November 17, 2008, letter is correct that the federal CPSIA phthalate limits do not apply to products manufactured prior to February 10, 2009 (an issue we do not address), then as to those products there can be no preemption of state law either, because there is no federal consumer product safety standard in effect and applicable to them.

Thus, A.B. 1108's phthalate standards are not preempted under section 26(a) of the Consumer Product Safety Act because, as to any given product, A.B. 1108 requirements are identical to federal requirements, and, as to some products regulated by A.B. 1108, there is no applicable federal standard.

Finally, CPSIA explicitly provides that neither it nor the Consumer Product Safety Act "shall be construed to preempt or otherwise affect any State requirement with respect to any phthalate alternative not specifically regulated in a consumer product safety standard under the Consumer Product Safety Act." (CPSIA § 108(d).) A.B. 1108 requires manufacturers to use "the least toxic alternative" when replacing phthalates, and replacement chemicals cannot include certain known or suspected carcinogens. (Cal. Health & Saf. Code, § 108939, subd. (a).) Congress expressly protected from preemption A.B. 1108's prohibitions on substitute chemicals.

Role of Proposition 65

Proposition 65 applies to products regulated by both A.B. 1108 and CPSIA and will continue to do so after those two statutes take effect, but we expect that it will have little practical significance because products that comply with A.B. 1108 and CPSIA would not, with a few possible exceptions, require a Proposition 65 warning. Thus, Proposition 65 actions should become largely unnecessary for products that comply with the other laws.

California's Proposition 65 requires that businesses provide a warning before knowingly and intentionally exposing persons to chemicals identified by the state as known to cause cancer or reproductive toxicity, unless the business can show that the level of exposure is below the level of significant health risk, as established under the statute and regulation. (Cal. Health & Saf. Code, §§ 25249.5-25249.13; Cal. Code of Regs., title 27, chapter 1 (§§ 25102-27001).) All of the Group 1 phthalates (DEHP, DBP and BBP) are listed reproductive toxicants under Proposition 65. Of the Group 2 phthalates, DIDP is a listed reproductive toxicant, while DINP and DnOP are not. One additional phthalate not covered by either A.B. 1108 or CPSIA, however, is a listed reproductive toxicant under Proposition 65: DnHP. Proposition 65 may be enforced by the Attorney General and district attorneys in the name of the People, by certain city attorneys, and by "any person in the public interest" who meets specific requirements, including issuance of a notice of violation and execution of a Certificate of Merit. (Cal. Health & Saf. Code, § 25249.7(c).)

Proposition 65 is not directly affected by A.B. 1108 or CPSIA. First, A.B. 1108 does not purport to repeal or limit Proposition 65, so compliance with both laws is required. Second, the warning requirement of Proposition 65 is not preempted by CPSIA, the Federal Hazardous Substance Act, or the Consumer Product Safety Act. CPSIA includes an express savings provision that protects Proposition 65 from preemption, stating that "Nothing in this Act [CPSIA] or the Federal Hazardous Substances Act shall be construed to preempt or otherwise affect any warning requirement relating to consumer products or substances that is established pursuant to State law that was in effect on August 31, 2003." (CPSIA § 231(b).) Furthermore, because Proposition 65 does not impose requirements on the "content" or "composition" of a product, and because it is not a "labeling" requirement,[3] it is not expressly preempted by section 26(a) of the Consumer Product Safety Act.

Thus, the requirements of Proposition 65, A.B.1108, and CPSIA on products containing phthalates will all coexist simultaneously. For example, a violation of A.B. 1108 or CPSIA that is also an independent violation of Proposition 65 can be enforced through Proposition 65. It is also conceivable that a toy or child care article containing phthalates below the A.B.1108 and CPSIA limits could still require a Proposition 65 warning. Based on our analysis of the products in question, however, we expect that the phthalate exposure from a toy or child care article that complies with the A.B. 1108 and CPSIA standards would be so low that no Proposition 65 warning would be required, with a few possible exceptions.

<u>Conclusion</u>

As of January 1, 2009, it will be illegal to sell, distribute, or manufacture toys and child care articles in California with greater than 0.1 percent of six specified phthalates, regardless of when or where the products were manufactured. The effective date of the federal CPSIA does not affect implementation of California's phthalate restrictions. Because A.B. 1108 will have

[3] Proposition 65 allows warnings to be provided through point-of-sale materials that are not "labeling." (*Chemical Specialty Manufacturers Assn. v. Allenby* (9th Cir. 1992) 958 F.2d 941; *People ex rel. Lungren v. Cotter & Co.* (1997) 53 Cal App. 4th 1373.)

been on the books for over 14 months before its phthalate limits take effect, we believe that industry has had sufficient time to prepare to comply with the requirements that take effect on January 1, 2009. The Attorney General, and other public enforcers, can and will enforce California's phthalate ban after that date.

If you would like to discuss this letter further, please contact Tim Sullivan at (510) 622-4038.

Sincerely,

TIMOTHY E. SULLIVAN
Deputy Attorney General

EDWARD G. WEIL
Supervising Deputy Attorney General

For EDMUND G. BROWN JR.
Attorney General

OK2006900364
Document in ProLaw

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RILA
RETAIL INDUSTRY LEADERS ASSOCIATION
Retail's Future...Educate, Innovate, Advocate

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December 4, 2008

Todd A. Stevenson, Secretary
Office of the Secretary
U.S. Consumer Product Safety Commission
Room 502
4330 East West Highway
Bethesda, MD

Re: Section 108 Phthalate Restrictions

Dear Mr. Stevenson:

Please accept the following comments from the Retail Industry Leaders Association (RILA) on behalf of our members in response to the Consumer Product Safety Commission's ("Commission" or "CPSC") Request for Comments and Information; Prohibition on the Sale of Certain Products Containing Specified Phthalates; Section 108 of the Consumer Product Safety Improvement Act ("CPSIA" or "Act"). Our members have discovered over the last year that, of all of the new restrictions found in the CPSIA, the restrictions on phthalates have the greatest impact on cost of production. As you are aware, the new phthalate restrictions, take effect on February 10, 2009. Because cost of production must be fully understood before retailers can even commit to purchase an item or determine the quantity to be purchased, it is with a certain sense of urgency that we offer these comments and hope that they will enable the Commission to expeditiously provide clarity on the following issues related to implementation of the new phthalates standards.

By way of background, RILA promotes consumer choice and economic freedom through public policy and industry operational excellence. Our members include the largest and fastest growing companies in the retail industry--retailers, product manufacturers, and service suppliers--which together account for more than $1.5 trillion in annual sales. RILA members provide millions of jobs and operate more than 100,000 stores, manufacturing facilities and distribution centers domestically and abroad.

Section 108(a) of the Act provides that "it shall be unlawful for any person to manufacture for sale, offer for sale, distribute in commerce, or import into the United States any children's toy or child care article that contains concentrations of more than 0.1% of ...DEHP, ...DBP, or ...BBP."

Section 108(b)(1) of the Act provides that "it shall be unlawful for any person to manufacture for sale, offer for sale, distribute in commerce, or import into the United States any children's toy that can be placed in the mouth or child care article that contains concentrations of more than 0.1% of ...DINP, ...DIDP, or ...DnOP."

Finally, Section 108(e)(2)(B) provides that "[i]n determining whether a children's toy can be placed in a child's mouth, a toy can be placed in a child's mouth if any part of the toy can actually be brought to the mouth and kept in the mouth by a child so that it can be sucked and chewed . . . If a toy or part of a toy in one dimension is smaller than 5 centimeters, it can be placed in the mouth."

Existing Inventory

RILA welcomes and agrees with the CPSC's legal analysis that the phthalate standards in the CPSIA do not apply to existing inventory. Section 108(d) provides that "[s]ubsections (a) and (b)(1) and any rule promulgated under subsection (b)(3) shall be considered consumer product safety standards under the Consumer Product Safety Act..."

Section 9(g)(1) of the Consumer Product Safety Act provides that "[a] consumer product safety standard shall be applicable only to consumer products manufactured after the effective date." 15 USC §2058(g)(1).

By providing that it is unlawful to offer for sale any product containing more than 1000 ppm of the banned phthalates after the effective date (February 10, 2009), Section 108(a) & (b)(1) begs the question—which product? However, by specifying that Section 108(a) & (b)(1) are consumer product standards under the Consumer Product Safety Act, we have a clue to the answer. If we read Section 9(g)(1) of the Consumer Product Safety Act, we find the answer—"products manufactured after the effective date." The CPSC's analysis on lead rejected this argument when applied to the new lead limits, precisely because those limits are under the Federal Hazardous Substances Act and the FHSA does not contain a similar provision to that found in Section 9(g)(1) of the CPSA.

Section 9(g)(2) of the CPSA also prohibits stockpiling. A stockpiling provision is irrelevant and unnecessary unless the phthalate limits of Section 108, now part of the CPSA, only apply to products made after February 10, 2009. Otherwise, if the phthalate limits apply to all products on the shelf as of February 10, there would be no reason to stockpile those products since a retailer couldn't sell them anyway. Having specifically provided for the possibility of stockpiling, Congress understood that risk existed, a risk that only exists if Congress also intended for the phthalate limits to apply prospectively to product made after February 10.

Inflatable Toys

The fundamental difficulty we encounter when applying the restriction of Section 108(b)(1) to inflatable toys is whether to measure the toy in its inflated or deflated state. Most if not all inflatable toys will be less than 5 cm in at least one dimension in their deflated state and would therefore be considered "mouthable."

RILA urges the Commission to determine that toys sold inflated, which are not designed or intended to be deflated and re-inflated for storage or between uses, should be measured in their inflated state. Likewise, toys that cannot be played with in a deflated state, and which when inflated do not easily deform or compress, should be measured in their inflated state. Just as the determination of whether a product is a toy at all depends in part upon its likely use, so should the determination of whether a toy is mouthable. The above-stated rule takes account of the fact that some inflatable toys are very unlikely to be mouthed in their deflated state. Section 108 does not speak directly to this issue. We can only conclude that this is precisely the sort of interpretive question left to the discretion of the Commission.

In the exercise of that discretion, we encourage the Commission to look kindly on the good work the European Commission's Enterprise and Industry Directorate General has undertaken to clarify the application of Europe's own phthalate restrictions. For example, the European Commission has said that large inflatable toys that are not easily compressed or deformed in their inflated state and that lose their play function when deflated should not be considered mouthable. It is noteworthy that the 5 cm rule found in Section 108(e)(2)(B) is borrowed directly from the European Commission's guidance, thus indicating the importance of this precedent on the Congressional deliberations that produced Section 108.

Aggregation

During the development of the CPSIA, there was significant discussion of whether the 1000 ppm limit on the banned phthalates would apply to each phthalate or to all of the regulated phthalates in the aggregate. For example, there was a difference of opinion about whether the effective limit on the six banned phthalates in a mouthable child care article would be 1000 ppm or 6000 ppm.

The final language of Section 108 seems to suggest that the limit is 1000 ppm for each of the banned phthalates. Hence, it seems that a mouthable toy or a child care article could legally contain as much as 6000 ppm of the 6 banned phthalates together, but no more than 1000 ppm of any one of those 6 banned phthalates. Likewise, non-mouthable toys could contain a total of 3000 ppm of the 3 banned phthalates. As a practical matter, the difference between 1000 ppm of the 6 banned phthalates and 6000 ppm in total of the 6 banned phthalates may have little impact on the functional characteristics of the product. Consequently, allowing 1000 ppm of each of the 6 banned phthalates will not promote intentional use of those 6 phthalates in a mouthable toy or child care article. However, this approach will permit the sale of those toys and child care articles that may contain as much as 1000 ppm of each of the banned phthalates.

Inaccessibility

Another point of confusion is whether the phthalate limits of Section 108 apply to inaccessible components. Inaccessible components by definition are not mouthable, and therefore, the interim ban on DINP, DIDP and DnOP in mouthable toys should not apply to their inaccessible components. Furthermore, the distinction between mouthable and non-mouthable toys indicates Congress's intent to take an exposure-based approach to regulation of phthalates. Since there is no risk of exposure to phthalates from inaccessible components, the phthalate limits of Section 108 should not apply to inaccessible components of any toys or child care articles.

Definitions

Toys - The definition of "children's toy" under Section 108(e)(1)(B) of the Act includes "a consumer product designed or intended by the manufacturer for a child 12 years of age or younger for use by the child when the child plays. However, Section 106 of the Act makes ASTM F-963 law wherein a toy is defined as "any object designed, manufactured, or marketed as a plaything for children under 14 years of age."

The inconsistency between the ASTM F963 and Section 108 age limits for toys, naturally leaves many wondering which age limit will control. The CPSC should apply the definition of "toy" under Section 108(e)(1)(B) of the Act to all requirements of the Act applicable to "toys," including the requirements of ASTM F963.

Section 101(c) of the Act provides that "[t]o the extent that any regulation promulgated by the Commission under this section (or any section of the Consumer Product Safety Act or any other Act enforced by the Commission, as such Act are affected by this section) is inconsistent with the ASTM F963 standard, such promulgated regulation shall supersede the ASTM F963 standard to the extent of the inconsistency." Hence, to the extent that the definition of "toy" in ASTM F963 is inconsistent with the definition of "children's toy" under Section 108(e)(1)(B) of the Act, the definition of "children's toy" under Section 108(e)(1)(B) controls.

Exemptions - Conversely, where the definitions and exemptions under ASTM F963 are not inconsistent with any regulation promulgated by the Commission, the Commission should consider the exemptions from the scope of "toys" covered by ASTM F963 as persuasive in its enforcement of the provisions of the Act applicable to "toys." For example, ASTM F963 specifically exempts sporting goods from its scope. If the same exemption is applied to other toy-related requirements of the Act, sporting goods will not be held to the phthalate limits of Section 108 of the Act.

The exemption of particular kinds of products from the scope of ASTM F963 reflects a refinement of the line between "toys" and "children's products" arrived at through the consensus standard development process. The consensus standard development process is critical to the private-public partnership upon which product safety depends. While the Commission will clearly take a stronger role in establishing standards for children's products, the Act itself in numerous instances presumes the continuation of the consensus standard development process. Unless clearly at odds with the will of Congress or the considered judgment of the Commission, the consensus standards that have been and will be developed for children's products should be credited in the Commissions enforcement policy.

To avoid having the exemptions swallow the rule, the Commission may consider more clearly defining the exemptions from the definition of "toys" under ASTM F963. For example, "sporting goods" might be defined as products designed and intended to be used in competitive recreation. As such, products such as basketballs, baseballs and baseball gloves, footballs, lawn games (horseshoes, bocce ball, badminton, or croquet), table games (foosball, air hockey, bumper pool, and shuffleboard tables), and sports protective equipment (helmets and protective pads) would be considered sporting goods, as opposed to toys, and would not be covered by the provisions of Sections 106 and 108 of the Act. However, they may nevertheless be considered "children's products" otherwise subject to all other provisions of the Act (testing, certification, lead limits, etc.).

Component Testing

Phthalate testing is expensive and time-consuming and should only be required when relevant. As the Act is currently written, it is unclear whether each component of a finished product must be tested or whether each component can be individually tested before being assembled into a final product. If every component of every toy and child care article must be tested for phthalates to support a certificate of compliance, enormous unnecessary costs and delays will be introduced. Meanwhile, the universe of materials where phthalates might be found is relatively small. For example, phthalates are used in PVC, but they are not used in polycarbonate plastics. Therefore, it makes no sense to require polycarbonate plastic components to be tested for phthalates. Likewise, wood, metal and rubber components will not contain phthalates. Hence, testing components made of materials that we know will not contain phthalates adds nothing to the safety of the product or assurance of its safety, but could add substantially to the cost of the product and the time needed to bring it to market.

RILA urges the Commission to create a list of materials from which toy and child care articles are made that require phthalate testing. Until such a list can be created, the Commission should only require that certificates of compliance be supported by testing accessible PVC components of toys and child care articles for phthalates.

Enforcement

RILA members are concerned that when the Commission provides guidance short of rulemaking on any provisions of the Act, state attorneys general may ignore that guidance. While state attorneys general provide a critical multiplier of enforcement capability under the Act, inconsistent enforcement among state attorneys general and between them and the Commission could render the Commission's considered judgment irrelevant. To avoid this calamity, RILA urges the Commission to include state attorneys general, where possible, in the process of developing guidance on enforcement of the CPSIA. Furthermore, RILA hopes that when the Commission establishes enforcement discretion guidance, that guidance will be widely distributed among state attorneys general. The Commission should also consider providing support and training to state attorneys general as they seek to enforce the Act. Finally, the Commission should make clear its expectation that the district court, in any action by a state attorney general to enforce the provisions of the CPSIA, will defer to the Commission's determinations about how the CPSIA should be and should not be enforced.

Conclusion

RILA and our members will continue to stay engaged in the Commission's process to provide further guidance on implementation of the CPSIA and we will take advantage of the opportunity to offer further constructive comments. Again, on behalf of our members, we thank you for the work that you have undertaken and for the opportunity to offer insights on how to successfully and effectively implement the CPSIA. Should you have any questions about the comments as submitted, please don't hesitate to contact me by phone at (703) 600-2046 or by email at stephanie.lester@rila.org.

Sincerely,

Stephanie Lester

Stephanie Lester
Vice President, International Trade

Stevenson, Todd

From: Stephanie Lester [Stephanie.Lester@retail-leaders.org]
Sent: Thursday, December 04, 2008 2:34 PM
To: Phthalates Project
Cc: Falvey, Cheryl; Andrew Szente; Casey Chroust; Katherine Lugar
Subject: RILA comments on phthalates
Attachments: Letter to CPSC on Phthalates 12 04 08.pdf

Please find attached comments by the Retail Industry Leaders Association on Section 108 of the Consumer Product Safety Improvement Act (CPSIA), "PROHIBITION ON SALE OF CERTAIN PRODUCTS CONTAINING SPECIFIED PHTHALATES". Thank you for your consideration of these comments. Please do not hesitate to contact me if you have any questions.

Sincerely,
Stephanie Lester

Stephanie Lester
Vice President, International Trade

Retail Industry Leaders Association
1700 N. Moore Street, Suite 2250
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CPSC/OFC OF THE SECRETARY
FREEDOM OF INFORMATION

2008 DEC -8 P 4:02

December 5, 2008

VIA FEDEX
Office of the Secretary
Consumer Product Safety Commission
4330 East-West Highway, Room 502
Bethesda, MD 20814.

Re: **Section 108: Phthalates in Children's Toys (Comment)**
Our Reference: 10609-0110001

Dear Sir or Madam:

This letter is submitted on behalf of our client, Speedo USA, a division of Warnaco Group, Inc., regarding Section 108 of the Consumer Product Safety Improvement Act ("CPSIA") concerning the prohibition on sale of children's toys containing specified phthalates. Subsection 108(a) prohibits the manufacture, import, distribution, or sale of "children's toys" or "child care articles" containing more than 0.1% of benzyl butyl phthalate (BBP), dibutyl phthalate (DBP), or di-(2-ethylhexyl) phthalate (DEHP) beginning February 10, 2009. Subsection 108(b)(1) prohibits, on an interim basis, the manufacture, import, distribution, or sale of "children's toys that can be placed in a child's mouth" or child care articles containing more than 0.1% of diisodecyl phthalate (DIDP), diisononyl phthalate (DINP)[1], or di-*n*-octyl phthalate (DnOP), beginning February 10, 2009.[2]

[1] DINP, which is used to soften some plastic toys and children's products, was the subject of a comprehensive study by the Consumer Product Safety Commission in 1998. That study concluded that few, if any, children were at risk from the chemical because the amount they ingest does not reach a level that would be harmful and stated that "the Commission staff is not recommending a ban on these products."

[2] Subsection 108(b)(2) also requires the Commission to begin the process of appointing a Chronic Hazard Advisory Panel (CHAP) "not before" February 10, 2009. The purpose of the CHAP is to review the potential effects on children's health of all phthalates and phthalate alternatives in children's toys and child care articles. The CHAP

The Consumer Product Safety Commission (the "Commission") has defined a children's toy as "a consumer product designed or intended by the manufacturer for a child 12 years of age or younger for use by the child when the child plays." Speedo USA produces a variety of swim goggles for adults and children. The goggles are sized as either "Adult" "Junior," or "Kid's." The Junior and Kid's goggles are designed to fit smaller, narrower faces. Speedo also makes "creature" goggles for children that feature sharks, reptiles, or similar whimsical overlays on the goggles. Representative pictures of Speedo USA's goggles are attached hereto.

For the following reasons, we strongly urge the Commission to clarify the definition of children's toys to specifically exclude swim goggles.

I. SWIM GOGGLES ARE NOT TOYS

A. Swim Goggles are Sports Equipment

Even where a particular model of goggles is specifically designed for children (i.e., the "creature" goggles), the activity they are used for – swimming – is considered a sporting activity.[3] As a sport, swimming involves the use of specialized equipment, such as swimsuits, swimcaps, earplugs, and goggles. Even in instances where swimming might be considered play, goggles are not required to engage in that activity. In this sense, goggles are akin to swimsuits: both items are designed for use while engaged in recreational activity, but neither item is intended to be played with, even if intended for use by a child.

Speedo USA's goggles are specifically designed for sport. Three sporting grades are available, depending on the user's activity level: The "Active" goggles are designed for use by recreational swimmers;[4] the "Performance" goggles, which are used for long training workouts, are intended for daily swimming exercise; and Speedo's "Competition" goggles are designed for the competitive swimmer. All of the goggles offer UV protection, an anti-fog feature, and a "speedfit" headstrap for reducing drag in the water. Some of the goggle models feature

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will recommend to the Commission whether to continue the interim ban and whether additional bans on phthalates or phthalate alternatives are needed.

[3] Many schools require swimming as part of the physical education curriculum, for example, and many schools and colleges have competitive swim teams. Similarly, many health and fitness clubs feature swimming pools and offer swimming classes as a form of exercise.

"aquasocket" technology, also designed to reduce drag. These features are available in all size ranges.

B. U.S. Customs and Border Protection Does Not Consider Swim Goggles Toys

U.S. Customs and Border Protection's ("Customs") classification of children's swim goggles provides further support for excluding them from CPSIA's definition of children's toys. Customs does not classify swim goggles for children as either toys *or* water sports equipment. *See* NY H86652 (Jan. 16, 2002) ("The swim goggles are not water sport equipment but rather are used for the protection of the eyes while swimming, usually in a pool . . . ."); *see also* NY G84446 (Dec. 5, 2000) (swim goggles contained in a youth combo snorkel pack are not toys or sporting goods). Rather, Customs consistently classifies swim goggles under HTSUS 9004.90.0000, which covers "spectacles, goggles, and the like, corrective, protective, or other."

Customs classifies swim goggles under heading 9004 regardless of whether the goggles are designed for children or adults. *See, e.g.*, NY F84727 (Mar. 31, 2000) (swim goggles classified as spectacles, goggles, and the like; not specified whether adult or children's); PD D83022 (Oct. 7, 1998) (same); NY C87534 (May 28, 1998) ("Swim Goggles (Junior)" classified as spectacles, goggles, and the like, protective or other . . .); NY 829617 (June 7, 1988) ("junior" swim goggles classified under HTSUS 9004.90.0000, as spectacles, goggles, and the like).

Even where the goggles are clearly sized or designed specifically for children, they are still not classified as toys. Customs ruling NY K80849 (Dec. 22, 2003) concerned swim masks in four styles – Spiderman, Teenage Mutant Ninja Turtle, Shark Man, and Ariel the Little Mermaid – whose intended use was for swimming. Customs classified the swim masks under 9004.90.0000, "spectacles, goggles, and the like," not as toys or sporting goods. Likewise, in NY J89436 (Oct. 3, 2003), the swim goggles at issue were part of a "Diving Game Combo" that included weighted "diving gators" and "diving sticks" that, when thrown into water, sink to the bottom for retrieval by a swimmer. The accompanying goggles were designed nearly identically to Speedo's swim goggles, with rubber eye gaskets and an elastic strap for securing to the head. The goggles were classified under 9004.90.0000, not as toys.

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[4] The "creature" goggles have whimsical character overlays with eyesocket and headstrap technology that is similar to the "Active" style adult goggles.

II. SPEEDO'S SWIM GOGGLES OFFER THE SAME FEATURES REGARDLESS OF SIZE

While there are design difference amongst the different models, Speedo USA's goggles offer the same features and protection regardless of size. The Adults, Junior, Kid's and "creature" goggles feature UV protection, anti-fog, and are latex-free. Moreover, all the Adult, Junior and Kid's versions within a particular model line possess the same fit, frame construction, eyesocket structure and adjustable silicon headstrap. Even the "creature" goggles have the same features as some of the adult goggles.

Aside from size, there are no design differences among the goggles despite their designations as Adult, Junior, or Kid's. The packaging of the various models is identical and they are not marketed to a particular age group. Thus, a small adult woman might choose the "Junior" or "Kid's" size, while a larger child may find that an Adult size fits him best.

III. CONCLUSION

Speedo USA's swim goggles offer the same features regardless of whether they are designed to fit adults or children. Even where a particular model's design indicates that it is intended for children, the goggles are not playthings. Swim goggles are sporting equipment, not toys. We therefore request that the Commission confirm that Speedo USA's goggles are not considered "toys" under the CPSIA and therefore not subject to the ban on phthalates.

Sincerely,

GRUNFELD, DESIDERIO, LEBOWITZ,
SILVERMAN & KLESTADT LLP

Alan R. Klestadt

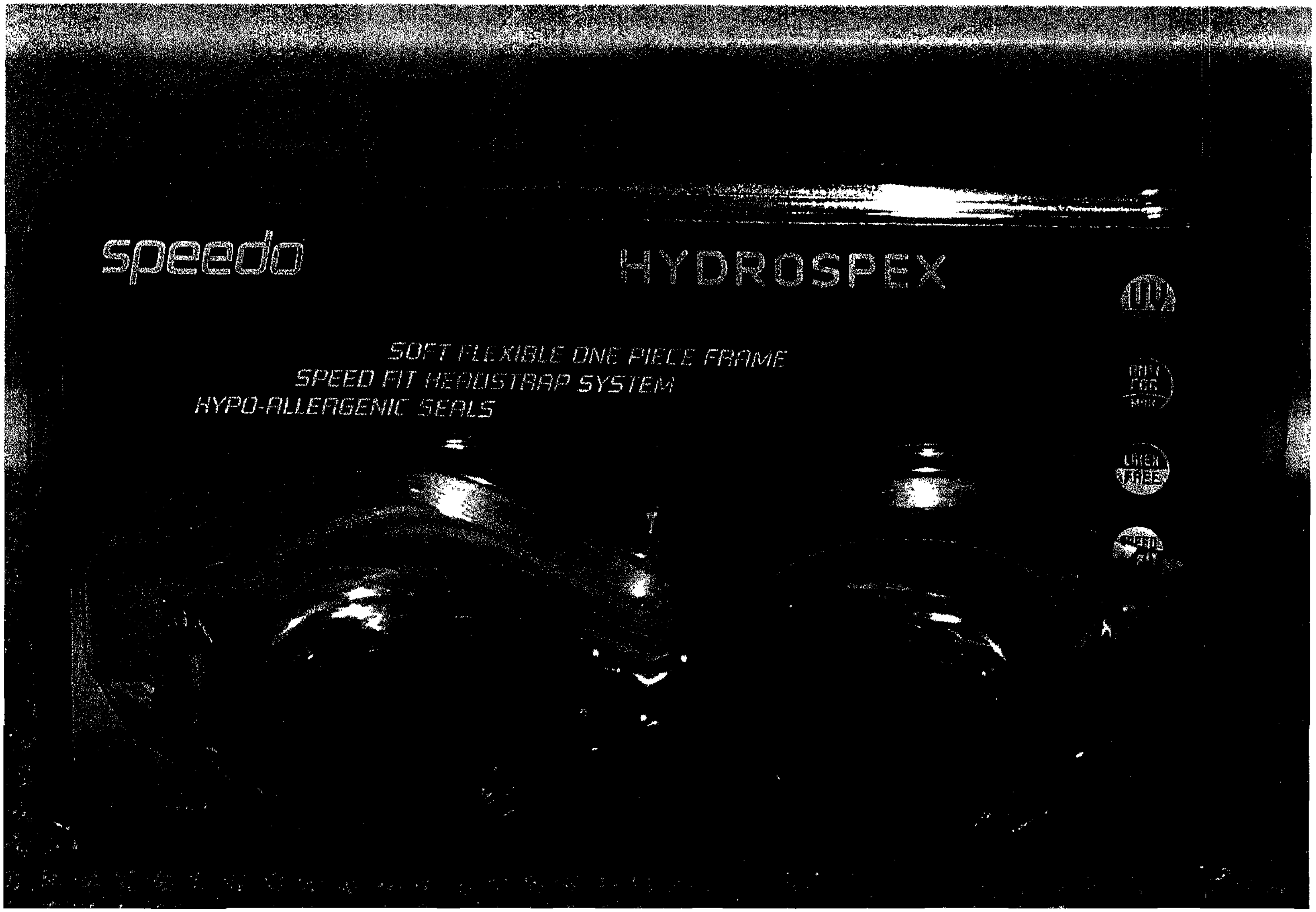
Alan R. Klestadt

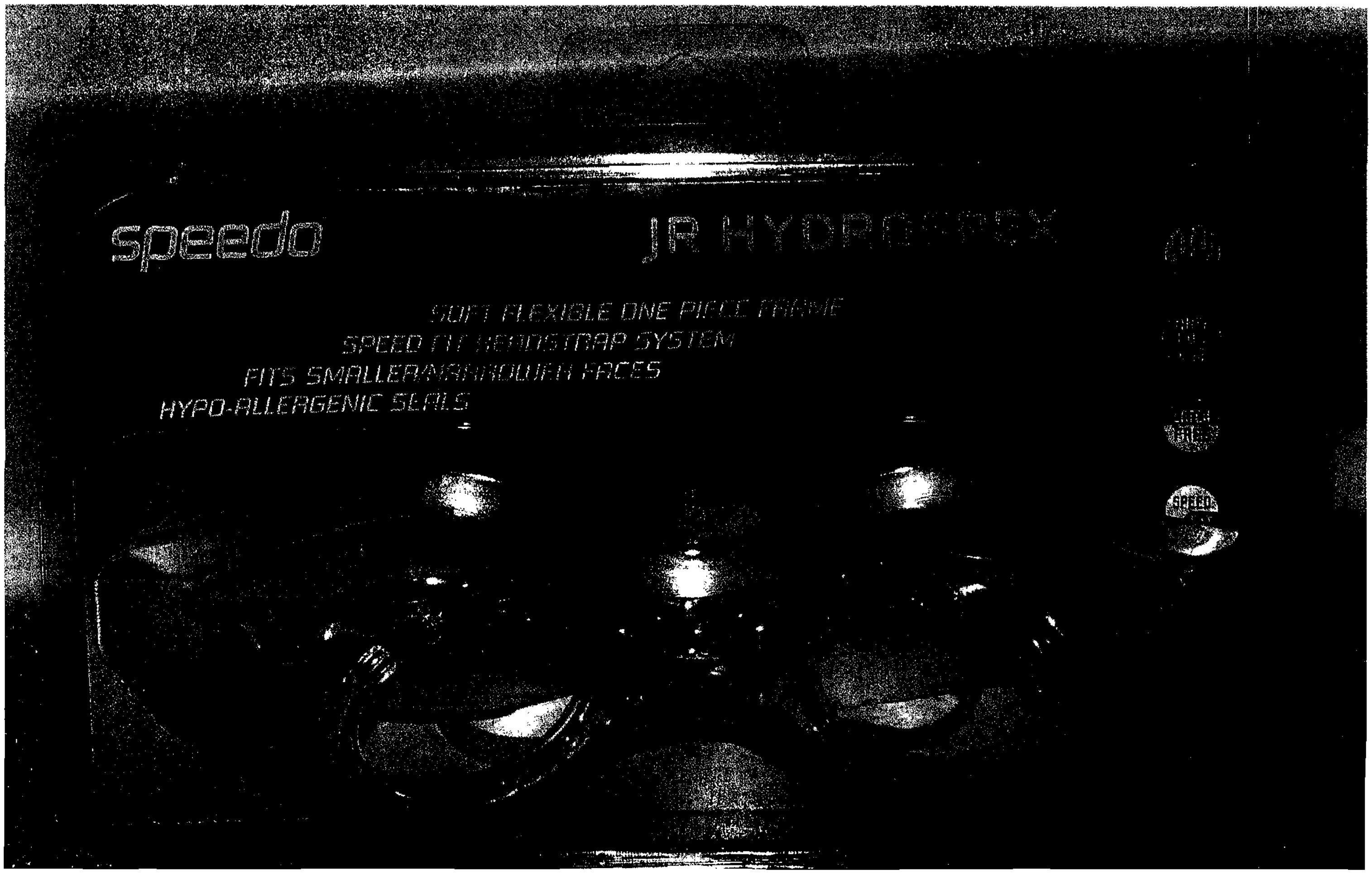
T. Gonzalez

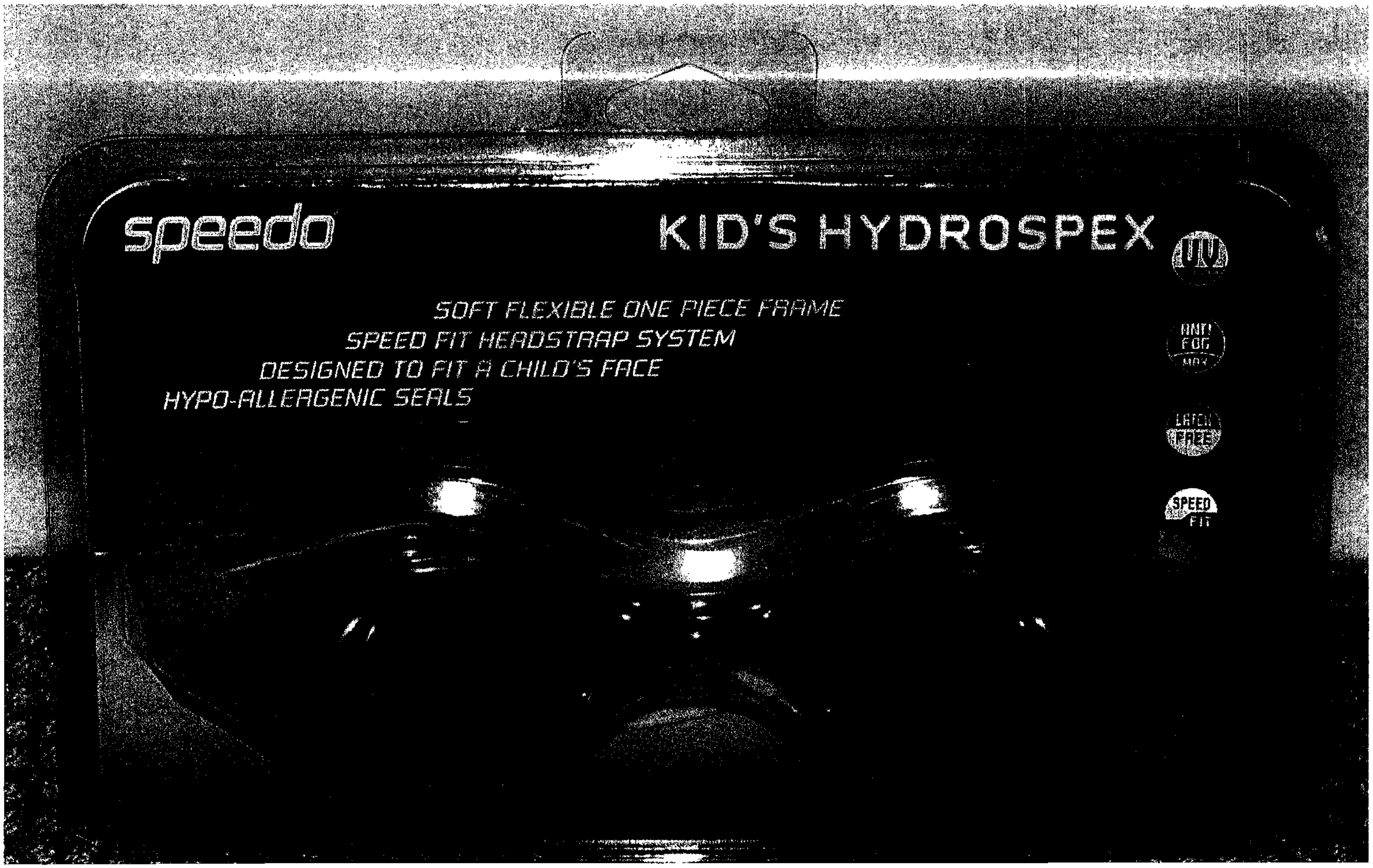
Tracey Topper-Gonzalez

Attachments

399029_1


speedo
HYDROSPEX
SOFT FLEXIBLE ONE PIECE FRAME
SPEED FIT HEADSTRAP SYSTEM
HYPO-ALLERGENIC SEALS
LATEX FREE


speedo
JR HYDROSPEX
SOFT FLEXIBLE ONE PIECE FRAME
SPEED FIT HEADSTRAP SYSTEM
FITS SMALLER/NARROWER FACES
HYPO-ALLERGENIC SEALS


speedo
KID'S HYDROSPEX
SOFT FLEXIBLE ONE PIECE FRAME
SPEED FIT HEADSTRAP SYSTEM
DESIGNED TO FIT A CHILD'S FACE
HYPO-ALLERGENIC SEALS
UV
LATEX FREE
SPEED FIT

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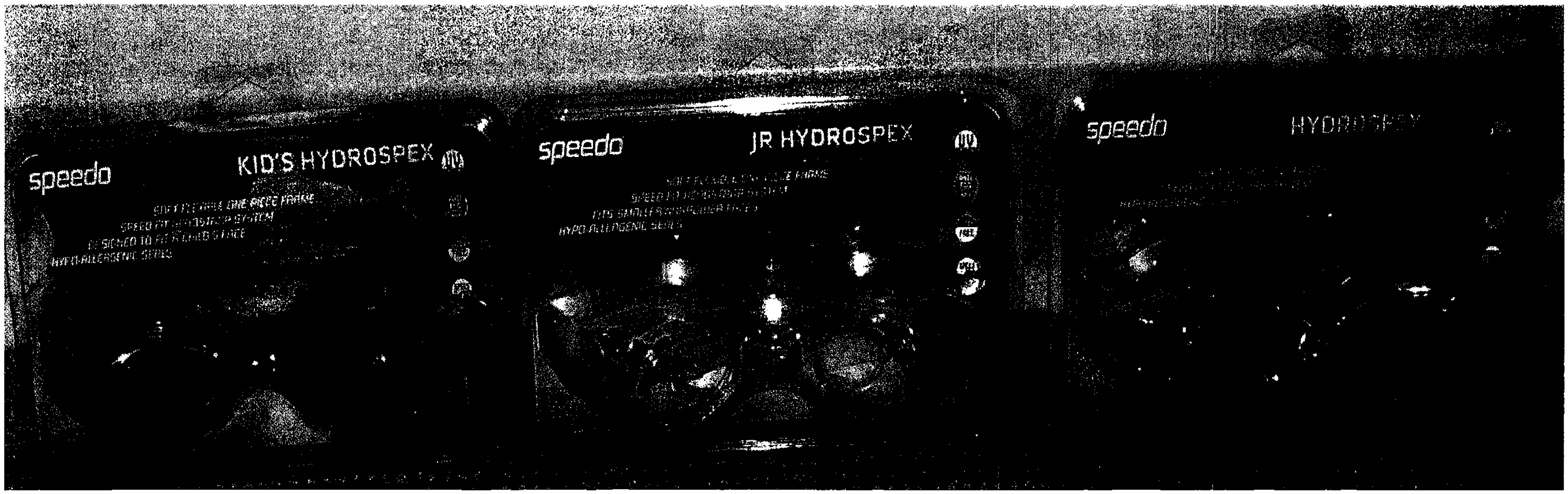
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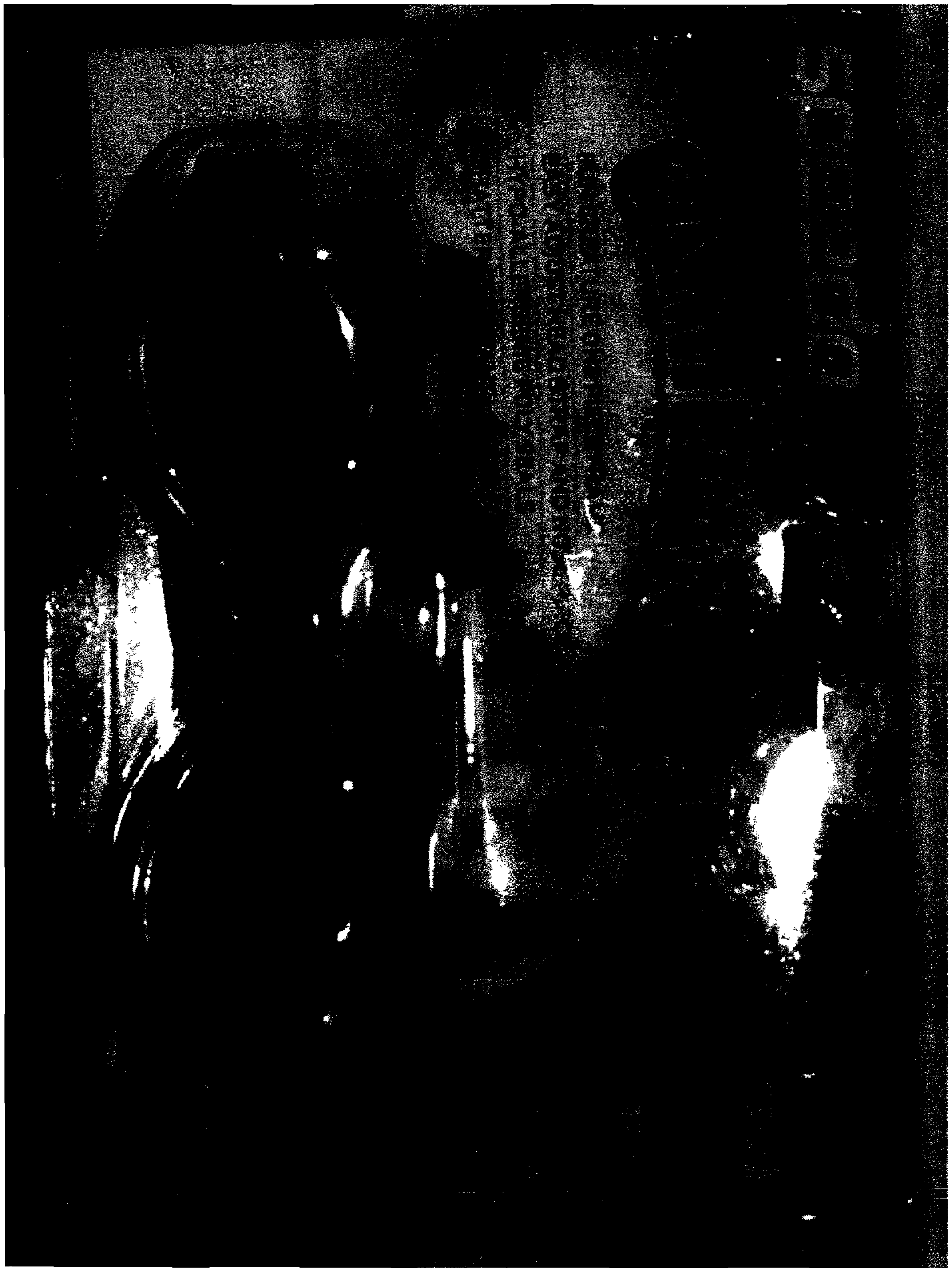


Sept 108 13

Carol Pollack-Nelson, Ph.D.
Independent Safety Consulting
13713 Valley Drive
Rockville, Maryland 20850-5402
(301) 340-2912
pollacknel@comcast.net

OFFICE OF THE SECRETARY FREEDOM OF INFORMATION
2008 DEC 11 P 1:09

December 8, 2008

Todd A. Stevenson, Secretary
Office of the Secretary
U.S. Consumer Product
Safety Commission
4330 East-West Highway
Bethesda, Maryland 20814

Dear Mr. Stevenson:

The purpose of this letter is to raise issues relating to phthalates requirements in the Consumer Product Safety Improvement Act (CPSIA).

As I mentioned in previous correspondence, I am a human factors psychologist specializing in the field of product safety. I work for both industry (manufacturers and industry groups) and consumer representatives (consumer advocacy groups and attorneys in litigation) equally. Regardless of who my client is, I use the same criteria for making any hazard determinations or determinations of intended user. The comments that I offer in this letter are not on behalf of any client. Rather, they represent my opinions as an independent safety professional.

In an effort to understand the scope of products that will be affected by the CPSIA phthalates requirement, I researched the wide variety of toy products available on the market and which are designed and intended for use by children ages 12 and younger. In addition, I rely on my experience evaluating toys and observing play behavior of children and "tweens." I also consulted the *Guidelines for Relating Children's Ages to Toy Characteristics* which lists a wide variety of toy classifications. Finally, I investigated definitions of the term "play." These include: (1) Exercise or activity for amusement or recreation; (2) the playing, action or conduct of a game; (3) to perform a musical instrument; (4) to cause (a phonograph or radio) to product sound or pictures (www.dictionary.com).

I'd like to begin by offering a general comment regarding the application of the phthalate requirements. Determining which products present a risk of injury due to ingestion of phthalates requires an understanding of how the risk presents itself. Namely, what are dangerous levels of phthalates and how are children exposed to these levels?

That is, which behavior(s) – e.g., mouthing and/or hand-to-toy followed by hand-to-mouth contact – expose a child to the risk? Furthermore, do different materials release phthalates differently? Do environmental conditions, such as heat and water, impact the release of phthalates?

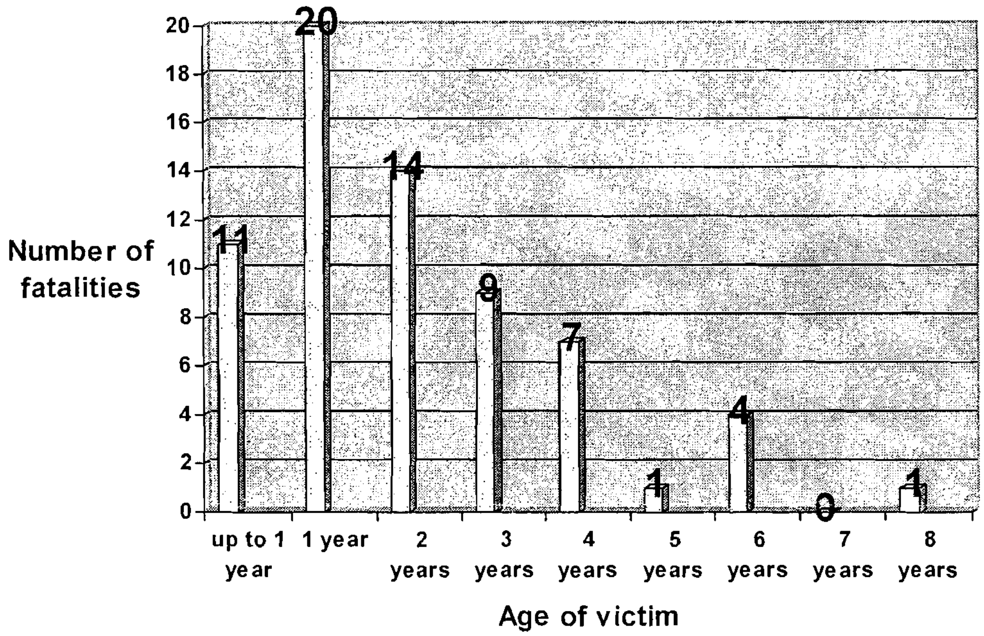
These questions need to be answered before determining how to apply phthalate requirements as it is difficult to know how to appropriately address a risk without understanding its scope and how it presents itself. Doing the reverse is likely to lead to over-coverage and application to products that do not pose a practical risk. The effects of such over-coverage could include unnecessary testing, certification, and product waste. I am assuming that the CHAP will address these issues and hope that they will draw on staff resources from Human Factors, Health Sciences, and Engineering Sciences.

While I am not familiar with the phthalate exposure risks associated with hand-to-toy followed by hand-to-mouth contact, I am knowledgeable about children's play and mouthing behaviors at different ages. Mouthing and play behavior of children are discussed in the behavioral literature. Additionally, there are numerous published studies that report on choking injury and fatality data.

"Play" behavior changes as children grow older. For very young children, their waking activities can largely be classified as play or caretaking (e.g., eating, grooming, sleeping, etc). Most interactions that they have with a toy (or non-toy) could be considered "play" or general exploration. For those younger than three years of age, play behavior is likely to include oral and tactile exploration. At this age, they handle everything and place objects in their mouths, often indiscriminately, for purposes of both oral exploration and also to alleviate teething. This behavior drops off as they become more mobile and as they differentiate and are able to utilize their products beyond simple sensory experiencing and cause-effect actions.

A study of CPSC choking fatality data involving children ages eight and younger and occurring from 2000 through October 6, 2008 confirms that children younger than three years are at risk of choking *(not yet published)*. Children under 36 months represented 67% of choking fatalities reported in this time frame. As is evident from the table below, two-year-olds were found to have the highest frequency of choking-related fatalities of any age group. Most choking incidents involved balls, which accounted for one-third of all incidents. In the remaining incidents, the offending objects were identified as balloons, screw or plug shapes, cap-shaped objects, pills, beads, coins, and a block. Additional cases involved miscellaneous plastic pieces such as a barrette, a pill vial, and a drawer stop, and unspecified foreign bodies.

Figure 1: Rate of Choking Fatalities by Age, 2000 - 10/6/08



By around three years of age, most children are moving out of the mouthing phase. Pre-schoolers are more focused in their play and use their toys as they are intended to be used, with less time spent with toys in their mouths and simply being carried around. They begin to engage in cooperative play; this is a peak time for role-play activities. Choking injuries and fatalities continue to be reported for three and four-year-old children. As seen in the figure, above, nine choking fatalities reported to the CPSC from 2000 through October 6, 2008 involved three-year-olds; seven involved four-year-olds.

By the time a child enters elementary school, at around five or six years, indiscriminant mouthing of toys and fingers is much less likely to occur for a number of reasons. First, elementary-aged children are no longer in a mouthing phase. They learn about their world and interact with their toys in non-oral ways. Second, because they are social, they are becoming aware of taboos that would be associated with mouthing behaviors. Mouthing toys and fingers would not only look "babyish," but may also inhibit social play if other children reject playing with toys that they had just put in their mouths. Further, for school aged children, not all waking behavior is considered play. Some of their time is spent doing chores, doing homework or learning, and socializing.

Choking fatalities in school-aged children is relatively uncommon. Of the six cases reported in children between five and eight years of age, half involved choking on balls. The other products involved were: a marker cap, a volume control knob, and a suction cup.

From the developmental literature and the choking fatality data, it is evident that children younger than three years are at the peak age for mouthing. However, mouthing does continue in some children to three and four years of age. Therefore, to address hazards posed by mouthing, chewing, and sucking on toys, I think it is most prudent to apply the phthalate requirements to any toy that is designed and intended for use by a child younger than five years of age. In addition, certain products that are known - both anecdotally and through injury and fatality data - to be mouthed by older children should be covered as well. The following are examples of items that older children place in their mouths:

(1) Jewelry (e.g., pendants, chains, and charms, but not earrings);

(2) Clip-on objects that are intended for children 12 and younger such as key fobs, backpack clips, and cell phone jewelry;

(3) Writing implements;

(4) Small balls

(5) Game pieces

(6) Barrettes and hair accessories;

(7) Items intended to be placed in the mouth such as musical instrument mouthpieces;

With regard to the interim ban on products that having a dimension that is smaller than 5 cm, I think that it is important to remember that the key factor(s) determining mouthing behavior is/are the child's age and/or, as noted above, type of product. Having one dimension that is smaller than 5 cm does not necessarily mean that the product likely to be sucked or chewed, particularly if that toy is intended for children ages 5 and older. For example, children are not likely to suck or chew on the neck of a guitar. And they are not likely to chew or suck on the slides that accompany a toy microscope. They are not likely to chew or suck on a volleyball net, ping pong paddles, baseball bases, etc. As noted above, there are some products that older children and adults do have a tendency to suck and chew. But for the most part, this is not a behavior we expect to see with most toys used by children aged five and older.

In addition to this list, if the CHAP finds that phthalates are leached from products when exposed to certain environmental conditions such as heat and water, then this list may need to be expanded to include other products like pool toys. Furthermore, if the CHAP determines that children can be exposed to phthalates by hand-to-mouth following hand-to-toy contact, then this list may need to be revisited. However, as already noted, finger sucking is not prevalent in children ages five and older. Therefore, those aged five and older are not likely to be exposed to phthalates in this way. In sum, if phthalate exposure occurs as a result of sucking and chewing behaviors, then I would suggest that toys that do not pose a risk of phthalate exposure be exempted from the requirement.

In addition to pertaining to toys that are intended for children up to 12 years of age, the CPSIA phthalate requirements also cover child care articles that are designed to facilitate sleeping or feeding in children younger than three years of age or to help with sucking or teething. It is obvious to me that this regulation covers items that are intended for use by children such as pacifiers, children's flatware, baby blankets, etc. It is also important that it apply to items that attach to a crib as a child who pulls to a stand is likely to mouth accessible components such as the top rail, a mobile or soother attachment.

Other products that are not intended to be directly used by the child, but that are likely to be handled (and mouthed) by a child should also be covered by the phthalate requirements. For example, an infant may be permitted to play with and mouth baby food storage containers, a diaper bag or bottle bag strap, etc.

It is less obvious to me whether or not the phthalate requirements should apply to products that are not directly used by the baby. For example, a baby food warmer that wraps around the exterior of a bottle is an example of a product that is used to facilitate feeding of a child younger than three years. The child does not mouth or have contact with this item. Is there a risk that a heated plastic food warmer will release sufficiently hazardous levels of phthalates onto the exterior surface of a baby bottle and such levels are likely to be transferred to the child's hands and subsequently, to the mouth?

Ultimately, an understanding of the ways in which phthalates are released is necessary to determine which products are likely to present a risk. I support the Commission's work to remove risks from children's toys and other products. It is my hope that this can be done in a meaningful way.

I greatly appreciate your consideration of my comments on this subject. If I am able to provide you with further clarification or assistance as the Staff develops a greater understanding of the issues, please do not hesitate to contact me.

Respectfully submitted,

Carol Pollack-N

Carol Pollack-Nelson

14 Sep '08

Nancy Nord, Acting Chair
U.S. Consumer Product Safety Commission
4330 East West Highway
Bethesda, MD 20814

Chair Nord,

Please enforce the Consumer Product Safety Improvement Act and make sure toys with over-the-limit levels of phthalates are off store shelves by February, 2009. Protect Kids, not chemical companies.

Sincerely,

Matt Cantor
Berkeley, CA

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National Council of the Churches of Christ in the USA

Washington Office

U.S. Consumer Product Safety Commission
4330 East West Highway
Bethesda, MD 20814

Dear Nancy A. Nord,

In this season of Advent, we, as Christians, stand with hope and great expectations as we commemorate the birth of Christ. As many children wait eagerly to celebrate this holiday season, parents will have to work extra hard to know what children's holiday products are safe. We are thankful that the Congress and President Bush recognized the importance of protecting children and future generations by passing the Consumer Product Safety Improvement Act (CPSIA). This legislation gives the Consumer Product Safety Commission (CPSC) mandate to set strong limits on lead and establish a precautionary ban on six classes of phthalates in children's products. Unfortunately, the CPSC has chosen to interpret this legislation in a way that weakens the very intention of this law by leaving children's products with phthalates on the shelves even after the legislation goes into effect. The CPSC's current interpretation of the bill will leave the most vulnerable members of our society—our precious children—at risk.

As Christians, we hear a moral call to care for the "least of these" and for future generations. We are also called to treat our bodies as holy temples and therefore be mindful of what we put into them. Last spring we, along with our partner organizations in state councils of churches and interfaith organizations, created "Christian Principles for a Healthy Body and Spirit" to express our Christian concern for toxic chemicals that jeopardize the health of God's Creation and vulnerable populations such as children and pregnant women. There is scientific evidence that links phthalates exposure with damage to children's reproductive development and other conditions, such as cancer, later in life. This threat to children undermines the very Christian principles that we set forth.

We call upon the Consumer Product Safety Commission to enforce the original intent of this bill to remove children's products with phthalates from store shelves by February 10^{th}.

Sincerely,

Cassandra Carmichael
Director, Eco-Justice Program Office
National Council of Churches USA

Stevenson, Todd

From: Candace Allgood [jscsmjra@yahoo.com]
Sent: Sunday, December 21, 2008 8:56 AM
To: Phthalates Project
Subject: Concerning new law

To whom it may concern,

I was very curious to know if I will be affected by this new law! On my site, www.Sonbeams.com, I sell a plastic dry erase Chore Chart. This is not a toy, but is a children's product.

If I would be affected by this, would I be responsible for testing, the company that sends me the final products (they only print on the boards), or the supplier of the boards to the printing company?

Then there's still the wet erase pen, clip to attach it, and magnets on the back...

This new law will put me under, if I'm the one having to pay for testing - which I wouldn't even know where to begin!

I also was about to order CD's. I have written songs to go along with Bible Verses, which would be taught to children. This would come in a plastic jewel case. Again, would I be responsible? And this would probably fall into the lead testing too...

I can see the good in protecting children, but this law is going to kill thousands of stay at home moms trying to make ends meet. We won't be able to sell our products, or buy homemade products for our children.

I would greatly appreciate any feedback/ assistance you could give me!
Candace Allgood

http://www.HeavenInOurHomes.com/
http://www.Sonbeams.com/

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Allentown TOY Mfg. Co.
HERTZ ASSOCIATES, INC.
725 N. 10TH STREET ALLENTOWN, PA 18102
1-800-523-9246
LOCAL : 610-434-6217
FAX : 610-434-7746
EMAIL : INFO@ALLENTOWNTOY.COM
WWW.ALLENTOWNTOY.COM

Charles Satterlee
Director Of Operations

Tuesday, December 23, 2008

Cheryl A. Falvey, Esq.
General Counsel
United States Consumer Product Safety Commission
4330 East West Highway
Bethesda, MD 20814

The Honorable Nancy Nord
Acting Chairman
United States Consumer Product Safety Commission
4330 East West Highway
Bethesda, MD 20814

Re: Questions Addressing Ambiguities Under The CPSIA as it Pertains to Small Business (Specifically, Small Businesses That Primarily Deal In Plush Products)

Dear Chairman Nord and Ms. Falvey,

This letter is intended to pose some fundamental questions that we (Allentown Toy Mfg. Co.) feel are unclear regarding the CPSIA. To begin, we would like you to know that we did not arrive at these questions lightly. We have read the following regarding the CPSIA:

- CPSIA
- The summary written for members of Congress regarding the CPSIA
- www.cpsc.gov (and all related FAQ pages regarding the CPSIA)
- We have contacted our Congressman, Rep. Charlie Dent, and his assistants including Chief of Staff George S. McElwee and Legislative Assistant, Collin Long.
- We have contacted Senator Robert Casey's office and have been in contact with Jennifer McCloskey.
- We have e-mailed and called to ask for appointments with your office, which at this time, have not been addressed or answered.
- We have read the letter from ARENT FOX to you dated, November 13, 2008.
- We have read the letter from you to ARENT FOX dated November 17, 2008.
- We have read the First Amended Complaint for Declaratory and Injunctive Relief filed in United States District Court For The Southern District Of New York by both The Natural Resources Defense Council, Inc. and Public Citizen, Inc.
- We have read statements by LAW 360 regarding the ambiguities and compliance issues.

Please understand, then, that we at Allentown Toy did not come to these questions lightly or with little thought. These questions are what we believe to be the core concerns that a business such as ours must address to ascertain if we can even stay in business or not after February 10, 2008. Please also understand that we do not write this letter in protest. We have been in business for nearly 61 years and we have always performed at levels above and beyond typical ethical and moral standards expected in business. A World War II veteran founded us and our company is directly responsible for the lives of over twenty-three people. We have always and continue to comply with any and all laws regarding our industry. That is our wish yet again. We are simply having a hard time understanding certain aspects of the CPSIA and we ask for clarification.

Our questions are:

1) On the CPSC website, there is a FAQ page.

This is the URL: http://www.cpsc.gov/about/cpsia/faq/108faq.html#108q8

Near the bottom of that page, the following question and answer is documented:

What certifications are required for children's toys and childcare articles subject to the phthalates ban?

Children's toys and child care articles manufactured on or after February 10, 2009, will need a general conformity certification based on a "test of each product or a reasonable testing program." Starting in September 2009, children's toys and child care articles will have to be certified based on third-party testing of the product by accredited third-party laboratories. The Commission must post its procedures for accrediting labs to test for phthalates in June 2009.

Posted 12/04/2008.

Based on the statement above, which again, was posted to the CPSC website regarding FAQ's for the CPSIA, any stock that can be verified as being in our warehouse before February 10 of 2009 will be exempt from the CPSIA testing mandate regarding Phthalates. We feel that this statement is confirmed in your letter dated November 17, 2008 and addressed to Ms. Georgia Ravitz and Mr. Scott Cohn from ARENT FOX LLP. In that letter, you stated that due to precedents such as ***Bowen Vs. Georgetown University Hospital 488 U.S. 204,208 (1988)*** show that the wording Congress chose to use regarding Phthalates in the Law excludes any existing stock manufactured prior to the February deadline to be exempt from testing. Is this true? Is our company correct in understanding that our current stock and any stock coming in before 02/10/2009 exempt from testing? Furthermore, are we currently allowed to stockpile stock before that date and will we be allowed to sell said inventory indefinitely after that date?

2) In the same question and answer above, the following statement rang out to us:

"Starting in September 2009, children's toys and child care articles will have to be certified based on third-party testing of the product by accredited third-party laboratories. The Commission must post its procedures for accrediting labs to test for phthalates in June 2009."
My next question is: When exactly does testing become mandatory? How can a company be compelled to hire a testing facility when the procedures for accrediting labs for the CPSIA mandate will not be posted until June 2009?

Additionally, we have contacted companies such as Bureau Veritas, who have told us that they are too busy and are not accepting new clients. How can a company who is trying to comply be held accountable if they can not hire a testing company?

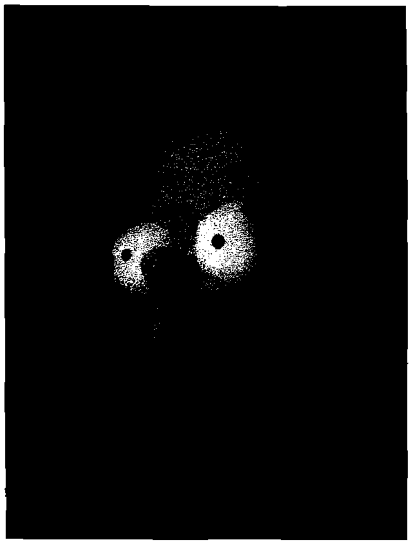
3) Can you explain to me, if the following, which is also posted to the CPSC website FAQ page regarding the CPSIA, is true, why are plush toys even being considered?

Do the phthalate limits apply to children's shoes or socks?

Shoes and socks are not considered to be children's toys or child care articles. See the Office of the General Counsel Advisory opinion (http://www.cpsc.gov/library/foia/advisory/318.pdf).

Posted 12/04/2008.

If socks and shoes are not considered to be "children's' toys" **OR** even to be "child care articles", how can plush be considered either as well? Plush toys are largely made up of the same material as footwear or socks. For instance, is a Homer Simpson plush slipper exempt but a teddy bear is not? See pictures below:



4) In the statement from the CPSC website in part one of this letter, the following statement is made:

"Children's toys and child care articles manufactured on or after February 10, 2009, will need a general conformity certification based on a "test of each product or a reasonable testing program."

My question is: What exactly constitutes a reasonable testing program? May we pick a few items from the same factory each year and have them tested, or is it every item we offer from here on out? If it is the latter, our business, which supports so many families and has never done anything wrong, not even a BBB complaint, will go out of business. Does each toy need a General Certificate of Compliance or does "PRODUCT" refer to the type of toy? Can we get one plush tested and therefore show that we are in compliance? We feel that it is enough to test certain items, even if they are chosen at random for us, and test those.

As you can see, our very future is at risk and we have no idea how to order for next year. Our hands are tied from doing future business right now which will also cripple us in the new year as we will run into a situation where our stock will decrease throughout the season to a point where we will have nothing to sell if we do not get more stock in soon.

One more question, if I may...

Does this relate to products specifically from China or does the CPSIA relate to all imported items?

Thank you for your hopefully speedy reply to these urgent questions regarding our possible future, or lack thereof.

Best Regards,

Chuck Satterlee
Director Of Operations
Allentown Toy Manufacturing Company
725 N. 10th Street
Allentown, PA 18102

CC: Congressman Charlie Dent; Chief Of Staff George S. McElwee ; Legislative Assistant, Collin Long ; Jennifer McCloskey; Nancy Homan; Senator Robert Casey

/8

Stevenson, Todd

From: Glatz, Linda
Sent: Wednesday, January 07, 2009 7:12 AM
To: Stevenson, Todd
Subject: FW: Message from Email Form

fyi

From: Information Center
Sent: Tuesday, January 06, 2009 2:39 PM
To: 'nermine@occupant.org'
Subject: RE: Message from Email Form

Thank you for contacting the U.S. Consumer Product Safety Commission CPSC). Please be advised your inquiry is being forwarded to the appropriate office within the agency.

Jft

Please be advised that you may obtain CPSC publications, recalls and general safety related information via our web site at www.cpsc.gov. Enter your topic in the search box and click the "go" button. You may also file an incident report or sigh up for our e-mail notification lists via the web site mentioned above. If you have additional inquiries, you may call our toll-free hotline at 1-800-638-2772, Monday- Friday, 8:30am to 5:00pm, Eastern Standard Time. Press 1 to begin and then 3 to speak with a representative.

From: emailform@cpsc.gov [mailto:emailform@cpsc.gov]
Sent: Monday, January 05, 2009 11:33 PM
To: Information Center
Subject: Message from Email Form

01/05/2009 23:32:54

Name = Nermine Hassan
Organization/Affiliation = A stay at home mom
Daytime Phone = 608 692 9977
E-mail address = nermine@occupant.org

Message = I would like to add my voice to I'm sure thousands if not a lot more regarding the new mandatory testing for all items made for kids under 12 that would destroy any chance for buying reasonably priced hand made products for our young ones. Please reconsider. I am a mother of two very little ones, and most of the things I buy for my little ones are hand made and are probably much safer than all the mass produced children' s plastic products out there. Thank you!

Stevenson, Todd

From: Melody Burch [melody_burch@msn.com]
Sent: Tuesday, January 06, 2009 10:40 PM
To: Phthalates Project
Subject: Subsection 108

Categories: Comment

To whom it may Concern,

I read that you have to recieve comments on law that stops the re-sale of used childrens clothing by Jan. 12, 2009. Hand-me-downs have been used for generations. Making a law like this is actually stupid. If your worried about lead, stop buying products from countries that use lead to make them, which sounds just as goofy as making a law to stop the re-sale of used products. Plus with alot of people wanting to lighten the load of what goes to the landfills, the re-sale of clothes and other items helps with that. Your also looking at alot of people losing their shops, and their employees back to looking for jobs. I think the economy is already having to work hard enough without a petty bill like this passing. Being a new mom, and a new wife, but always have been on the poor end of things, I've always recieved hand me downs, and never had a problem. My little brother as well, and while I was pregnant, several women gave me clothes for him, since I didn't have the money to buy clothes even with a job, and my husband working as well. Not to sound to blunt, but yeah, this law sounds more and more like a way for the corporations to make up for money they loss, and the government that was made for the people, by the people, of the people is giving in.

Thank You,
Melody A. Sharpnack

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01/07/09

Regarding:
Prohibition on the Sale of Certain Product Containing Specified Phthalates
Section 108 of the Consumer Product Safety Improvement Act (CPSIA)
Request for Comments and Information

Dear Commission,
OMI welcomes and applauds this new piece of legislation as much needed public protection from harmful phthalates found in common textile products today, protection that has been a guiding principal here at Organic Mattresses Inc. since our inception.

To ensure that OMI products meet our own strict purity standards, OMI has third party tested for the presence of phthalates, aldehydes, VOC's and many other toxins for the past three years. OMI has not limited itself to children's products, but tests ALL products quarterly and has consistently tested well below the lowest limit set by the Commission.

As you know the textile industry has been thrown into a panic to meet the requirements of the newly passed Consumer Product Safety Improvement Act. This is a broad piece of legislation, which we understand has yet to be finalized. It is greatly appreciated that the Commission is hearing comments from companies such as ours.

As comment I would like to convey and ask the following:

- Test for emissions rather than content. This will ensure child protection and significantly reduce costs for manufactures. Please see the following website for test criteria: http://www.aqs.com
- CPSC's web list of approved test facilities does not provide a facility that covers all required tests for mattresses. If a CPSC approved facility is not available will a company be in violation. In addition, facilities will be backlogged, will this wait time be forgiven.
- Is cotton and wool a confirmed exception to test requirements for phthalates as well as lead?
- Organic products produced with NOP, GOTS, and Oeko Tex etc. raw materials meet organic standards that prohibited use of chemical inclusion, processes and proximity; these should be excluded from testing. Please consider comments submitted by Organic Trade Association (OTA) regarding organic products.

I look forward to your reply.

If you have any questions or would like to discuss these points more extensively please don't hesitate to call.

Sincerely,
Virginia L. Tippey
Compliance Officer, OMI
800.951.9196
virginia@omifactory.om

21

MATTA

Matta Products Limited

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6 Canon Place, Pakuranga
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office@mattaproducts.com
www.mattaproducts.com

Office of the Secretary
Consumer Product Safety Commission
Room 502
4330 East-West Highway
Bethesda
MD 20814

7 January 2009

Re Section 108: Phthalates in Children's Products

Matta Products Ltd and our Californian subsidiary Matta Products LLC manufacture, supply and install playground surfacing to schools, park authorities and other various customers throughout the United States and other markets worldwide. Our wider company oversees the recycling of around 10,000 tons of post consumer and post industrial waste plastic annually, of which a significant portion, is PVC.

The Play Matta™ surfacing system consists of a rubber shock pad base which is covered by interlocking PVC tiles, each measuring 20" x 20" x 1" and weighing over 6 lbs. The tiles are heat welded together on site to provide an extremely resilient unitary surface. This ISO certified system is manufactured and installed to meet all relevant ASTM specifications including F-1292 (Impact attenuation) F-1951 (Accessibility around playground equipment) and the new standard on lead in Children's PVC toys. Our surfaces do not degrade and are guaranteed for a minimum of 6 years with extension options available at the completion of this period.

One of the key features of the Play Matta™ system is its high content of recycled materials. The shock pads are manufactured from rubber waste from tire manufacturers and the PVC tiles have traditionally been manufactured from post industrial PVC waste. PVC was chosen many years ago due to its resiliency, ease of handling, availability of recyclable sources and the fact that the end product in itself can be (and is) recycled.

According to previous advice from the CSPC, a playground surface is "intended for use by children" and it therefore falls into the category of children's toys.

Up until the new restrictions on phthalate use, Play Matta™ PVC tiles were produced from clean, contaminant free post industrial PVC waste. This waste was sourced predominantly from the medical supply industry from companies manufacturing items such as blood and plasma bags, dialysis tubing etc. As these companies are still using (predominantly) DEHP, we are no longer able to use this source of PVC. In fact we have been unable to find any source of PVC scrap worldwide, that does not contain one of the banned phthalates, in quantities sufficient to meet our production requirements. We are also aware that many manufacturers of PVC items (including US manufacturers) are now having problems finding uses for their unwanted PVC waste. As a result a valuable resource will no doubt end up being down-cycled into a much lower value product, sent to landfill, or incinerated.

The effect on Matta is that we now have to use virgin PVC, plasticized with a compound that is not on the banned list. As our company was built around recycling, this is seen as a major step backwards, but a necessary one, in order to retain our US market. We find this ironic when it is a stated goal of the EPA to encourage recycling.

Matta is totally committed to providing a safe environment for children at play. However, we are interested in the justification as to why the medical industry can continue to use these banned substances in for example, neo-natal plasma bags where the same substances are banned in what is essentially a safety flooring product.

Ideally we would like to see a standard more similar to the European equivalent where phthalate restrictions are in place only for children's articles that can be placed in a child's mouth. In addition, or as an alternative, we would like to see the inclusion of the list of articles, to which the prohibition does not apply, as with the Directive of the European Parliament and of the Council on the Safety of Toys. Specifically 2 (a) in Chapter 1, Article 1 "playground equipment intended for public use" is exempt.

We are following developments around phthalate use with a keen interest, especially from the point of view of a recycler and manufacturer. We look forward to the opportunity to comment further on any notices of rulemaking proceedings in the Federal Register and hope we are able to make a valuable contribution to this process.

Yours sincerely
Matta Products Ltd

Paul Thomsen (B.Chem E)
Business Development Manager

paul.thomsen@mattaproducts.com
ph +6421 976 299
fax +649 577 4929

Stevenson, Todd

From: Paul Thomsen [paul.thomsen@mattaproducts.com]
Sent: Tuesday, January 06, 2009 9:57 PM
To: Phthalates Project
Subject: Section 108: Phthalates in Children's Products.
Attachments: CPSC Phthalate Submission.pdf

Please find comments attached.

Can you please also confirm receipt of this message by return email.

Regards

Paul

MATTA

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www.mattaproducts.com

*** Consumers Union * Consumer Federation of America ***
*** Kids in Danger * National Research Center for Women & Families * Public Citizen * Union of Concerned Scientists * U.S. Public Interest Research Group ***

January 7, 2009

Honorable Nancy Nord
Chairman
U.S. Consumer Product Safety Commission
4330 East-West Highway
Bethesda, Maryland 20814

Dear Chairman Nord:

Our groups, representing consumer, scientific, and public health interests, write to urge the Commission to provide guidance and clarity and to **immediately** dispel misinformation now circulating among entities regulated under the Consumer Product Safety Improvement Act (CPSIA). The CPSIA, a landmark new law, will go a long way toward improving the safety of products brought to the marketplace and restoring consumer confidence in the products they buy. Some small businesses have expressed concern about the lack of guidance and information from CPSC about the implementation of the CPSIA. The vacuum of implementation information, as well as the proliferation of misinformation regarding actual testing requirements and the cost of testing is leading to confusion and fear. The public counts on the CPSC to protect them from dangerous products. Now CPSC must take the initiative to allay their fears by providing prompt, common-sense, and explicit interpretations regarding exemptions to CPSIA stipulations, guidance as to the realistic cost of testing, and education regarding compliance with the CPSIA for retailers, including thrift and consignment stores.

As you are aware, events over the last several years have shattered public confidence in the safety of products sold in the United States -- particularly children's products. The year 2007 was dubbed by consumer groups and the media as the "year of the recall," with 473 recalls administered by the CPSC. These recalls included children's toys pulled from the market due to the presence of lead paint, cribs that collapse and toys with dangerously strong magnets that seriously damage children's stomach lining when swallowed, and even toys with toxic chemicals that can induce comas if swallowed. The year 2008 fared even worse, with 563 recalls, including nearly 8 million toys.

Although laws have existed with minimum safety requirements for toys and other children's products, these products were not required to be tested before sale. The many recalls of dangerous and toxic toys made it clear that the system was, in fact, broken. Fortunately, Congress answered the call to address these concerns, and on August 14, 2008, President Bush signed into law the Consumer Product Safety Improvement Act ("CPSIA"). Both the House and Senate passed this important bipartisan reform measure by overwhelming votes. The Senate passed the CPSIA by a vote of 89 to 3, and the U.S. House of Representatives an overwhelming vote of 424-1. The CPSIA passed after lengthy and careful deliberation by Congress, with many hearings and extensive input from all stakeholders. Consumers, manufacturers, and retailers are now counting on the Commission to properly implement the law that Congress has passed.

The CPSIA requires what many consumers already thought was law—that certain children's products must be tested for safety **before** they are sold. This is one of the most significant steps leading to a safer marketplace for our children. This law also recognized consumers' expectations, that toys and other children's products on store shelves would be safe – and certainly not harmful – to such a vulnerable population.

<u>The CPSC Must Quickly Provide Guidance and Clarify Any Exemptions Regarding the New Law's Safety Testing and Certification Requirements</u>

Given the authority granted under the CPSIA, the CPSC has a critical responsibility to implement the new law effectively, fairly, clearly and in a timely manner. We are pleased to see the rapid pace at which the Commission is implementing many parts of this important new law. The CPSIA already presents a common-sense approach to many key product safety issues. Congress itself acknowledges within the legislation that while certain products create a risk, some products and materials will be granted exemptions from the pre-testing requirements if they do not present a risk of harm. (CPSIA Section 101 (b)(1)).

We are concerned, however, that the CPSC has been slow to respond to a growing chorus of confusion and concern expressed by product makers about the product testing and certification requirements of the CPSIA. Much of the confusion about these requirements has been expressed by smaller business owners. In the four months since passage of the CPSIA, the Commission has failed to use the process included in the law in Section 101(b)(1) to provide clarity for industry about common sense testing and certification exclusions for products and materials that will not harm the public health. Although some preliminary information regarding exclusions to the lead standard was released on December 24, we strongly urge the CPSC to move quickly to clarify how this new law applies to certain products or materials that do not present a risk to children or the public. However, CPSC should only grant exclusions to this provision that are scientifically well supported to have no negative impact on public health and safety.

While certain segments of industry are raising valid questions about the new safety testing requirements under the law, other industry statements and reports about the impact of the law overstate and/or misstate important aspects of the requirements of the new law. The CPSC can – and must – address valid concerns, and act to quell misinformation surrounding the new testing requirements. Congress has spoken clearly, and now the CPSC has the responsibility to use the tools already provided to it by the legislation and provide the necessary, accurate and important guidance to all interested parties to further the timely and effective implementation of the CPSIA.

Awareness and Information Campaign for Small Manufacturers, Retailers and Secondhand Sellers

It is within the CPSC's discretion to inform smaller manufacturers and retailers how to comply with the new legal requirements. We strongly recommend the launch of an information and education campaign that would help regulated entities to comply with the CPSIA, thus supporting the CPSC's compliance efforts. CPSC must work with second-hand sellers to ensure compliance with the intent of the CPSIA – keeping dangerous products off shelves and out of our homes – while also presenting common sense solutions for these stores. Once CPSIA is fully implemented, the secondhand market will be safer since unsafe products will be taken out of the stream of commerce.

However, to be clear, exemptions should not be made to the law's requirements based upon the size of the product maker or seller (e.g. based upon production output or numbers of products imported). To the contrary, there are many reasons to include such entities. As evidenced by many product recalls, there have been dangerous or toxic products recalled involving manufacturers who produce less than 50,000 units per year. Here are just a few examples:

http://www.cpsc.gov/cpscpub/prerel/prhtml09/09068.html

http://www.cpsc.gov/cpscpub/prerel/prhtml08/08579.html

http://www.cpsc.gov/cpscpub/prerel/prhtml09/09028.html

As well as recalls involving products made in the United States:

http://www.cpsc.gov/cpscpub/prerel/prhtml09/09052.htmlhttp://www.cpsc.gov/cpscpub/prerel/prhtml08/08253.html

http://www.cpsc.gov/cpscpub/prerel/prhtml06/06262.html

There is also much misinformation circulating about the cost of testing for compliance with the requirements of the CPSIA. Here again, the CPSC can allay fears among the business community by publishing typical testing costs based on a survey of laboratories accredited to conduct such testing.

Our children deserve the safest products possible. The bipartisan law approved by Congress in 2008 provides that safety. It would be tragic if your Commission, by failing to provide the appropriate guidance and exemptions, failed to effectuate this important new law.

Sincerely,

Rachel Weintraub
Director of Product Safety and Senior Counsel
Consumer Federation of America

Janell Duncan
Senior Counsel
Consumers Union

Donald Mays
Senior Director, Product Safety and
Technical Public Policy
Consumers Union

Ami Gadhia
Policy Counsel
Consumers Union

Ed Mierzwinski
Consumer Program Director
U.S. PIRG

Nancy A. Cowles
Executive Director
Kids in Danger

Elizabeth Hitchcock
Public Health Advocate
U.S. PIRG

Celia Wexler
Washington Representative
Scientific Integrity Program
Union of Concerned Scientists

Diana Zuckerman
President
National Research Center for Women & Families

David Arkush
Director, Congress Watch
Public Citizen

cc:
CPSIA Conferees
Members of Senate Commerce Committee
Members of the House Energy & Commerce
Leadership of the United States Senate and the U.S. House of Representatives

Stevenson, Todd

From: LaVonne Fishell [lfishell@cfl.rr.com]
Sent: Wednesday, January 07, 2009 8:26 PM
To: Kelli Nava; Phthalates Project
Subject: Used children's clothing

Categories: Legal comment

To Whom answers this email:

My understanding is that children's used clothing will be affected. This would be very crippling in a time when a recession is in progress and needy parents depend on buying used clothing which has been created before Feb 10, 2009 and have been laundered many times.

Please give me a definite answer as to how internet buying and/or consignment shop buying will be handled as of and after Feb 10, 2009. As MANY small businesses and charitable organizations depend on this and there would be a very low risk in used clothing unless it was stated what Mfg to avoid selling.

Thank you for your quick response.

LaVonne Fishell
4047 Teriwood Avenue
Orlando, FL 32812

lfishell@cfl.rr.com

Stevenson, Todd

From: Simon [dik3ann@tds.net]
Sent: Thursday, January 08, 2009 7:41 AM
To: Phthalates Project
Subject: children's books should not be banned under this regulation

There is some concern that modern vintage and antique children's books may be included in this ban...most of these are collected by adults, some are shared with children but seldom with athose s young as children who are teething .

May I point out that a book read to a child this age would be held by a parent and is not considered a plaything.. Please do not include children's books in the banned list. Thnk you, Ann Simon

Stevenson, Todd

From: Jim Coleman [jcoleman@hedstrom.com]
Sent: Thursday, January 08, 2009 12:03 PM
To: Phthalates Project
Subject: Phthalates in consumer products

Responding to your request for comments

- Considering that phthalates may have uses other than as plasticizers for PVC, are there any other types of children's toys, toys that can be mouthed, or child care articles that may contain phthalates or phthalate alternatives?

At Ball, Bounce & Sport w e have found out the hard way that product packaging may contain small amounts of prohibited phthalates. These may leach or bleed into 6P compliant soft plastics in sufficient quantity to cause non-compliance in the product. It is extremely difficult to maintain the integrity of 6P compliant materials throughout the entire factory-to-consumer process chain. We have changed our specifications to require 6P compliance for packaging used for 6P products.

We feel the CPSC should also investigate other common household products as likely sources of phthalate exposure for humans. The potential for exposure to phthalates via ingestion of cosmetics, hand lotions, soaps, detergents, pharmaceuticals, and nutritional supplements, and for exposure via inhalation of spray air fresheners, hair sprays, lubricants, waxes, cleaning materials, and insecticides is far greater than the potential exposure from toys and children's products.

Any evaluation of potential phthalate hazards should include exposure from all potential sources, not just PVC toys. If the withdrawn Washington State phthalate legislation had applied to all consumer products instead of toys it would have been illegal to sell autos and many other consumer products there!

The CPSIA lead content regulations have a scientific basis with historical data to back them up. However, the CPSIA phthalate regulations were based on the emotions of the current political climate rather than on facts. The EU has determined that they overreacted in their ban of DINP, but they are unwilling to remove the ban because of potential political fallout.

Best regards,
Jim

Jim Coleman
Quality & Compliance Manager
***Ball Bounce & Sport, Inc.,* Hedstrom**
WORLD HEADQUARTERS
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phone - 1.419.282.5505
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Meet and Exceed Customer Expectations Every Time
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"Luck is where opportunity meets preparation"

Stevenson, Todd

From: tnq113@aol.com
Sent: Thursday, January 08, 2009 4:57 PM
To: Phthalates Project
Subject: Comment on new law

Categories: Legal comment

Dear Sir/Madam:

I understand the reason behind the Consumer Product Safety Improvement Act, but I do not think it has been thought through completely. To test all children's clothing and accessories made before February 10th would be absolutely absurd and wasteful. I am part owner of a consignment clothing and home decor business. We have seen an increase in business due to economic conditions in this country. To throw this fuel on the fire, would be outrageous. More thought needs to go into this law. It needs to be amended to state clothing manufactured after Feb.10, 2009. Then when it is resold, everyone will know that it has already been tested.

Do you have any idea what this could do to the Salvation Army, Catholic Social Services, Goodwill? There are many people all over this nation, along with my customers, that depend on buying their children's clothes through this avenue. Tons of grandmothers buy their grandchildren extra swings, bouncy seats, carriages, highchairs, etc through consignment. Churches have fairs and raise tons of money selling children's clothing and products. What a waste this would be in this age of recycling! The landfills will fill up even faster. There is a definite trickle-down effect regarding this matter.

When my database of 1500 customers find out about this, they are going to be totally up in arms, as we were. I am asking you to please think about this - think of the ramifications. While trying to keep a child from being poisoned, you are keeping millions from being clothed.

With best regards,

Teresa N. Quarles
Augusta, GA

Stevenson, Todd

From: Tim Zacharewski [tzachare@msu.edu]
Sent: Thursday, January 08, 2009 8:14 PM
To: Phthalates Project
Subject: Section 108: Phthalates in Children's Products
Attachments: CPSC Questions 010809.doc

Please find attached my responses to questions that may be of interest to the CPSC. Please feel free to contact me if further information is required or if I can be of any other assistance.

Sincerely,

Tim Zacharewski

Tim Zacharewski, Ph.D.
Michigan State University
Department of Biochemistry & Molecular Biology
501 Biochemistry Building
Wilson Road
East Lansing, MI 48824-1319

TZ office tel: 517-355-1607
TZ lab tel: 517-353-1944
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NFSTC fax: 517-432-2310
BMB fax: 517-353-9334

NFSTC tel: 517-432-3100
BMB tel: 517-355-1600

Science Roundtable

Q: What is the significance of metabolized phthalates found in urine?

A: Phthalates are excreted from the body via the urine. Therefore the presence of phthalate metabolites in the urine of children and adults is not cause for alarm. This represents a common mechanism used to eliminate synthetic and endogenous chemicals from the body. However, many recent studies have cited concerns for phthalates as a result of traces found in human urine. These concerns are misleading because they do not acknowledge that urine is a common mechanism to rid the body of many chemicals, including both synthetic and endogenous chemicals. Phthalates are readily metabolized in the body, and effectively eliminated from the body via urine. There is also well-established evidence that phthalates do not accumulate in the human body or the food chain.

Within the past decade, scientists have developed extremely sensitive technologies to test for trace levels of chemicals in a variety of matrices. For example, approximately 1 part per billion of metabolized phthalates can be detected in urine samples. With these advanced biomonitoring techniques, the US Centers for Disease Control (CDC) has been able to perform tests measuring the amount of phthalates found in human urine. These test results indicate that the phthalate levels found were well within safe limits established by the EPA, and are not cause concern. [1] It should be noted that the detection of ppb levels of a chemical in urine does not mean it has any biological significance.

More specifically, the CDC's 2005 Third Biomonitoring report states that, "finding a measurable amount of one or more phthalate metabolites in urine does not mean that they cause an adverse health effect. Whether these levels of phthalate metabolites are cause for health concern is not yet known; more research is needed. These levels of phthalate metabolites in urine provide physicians with a reference range so that they can determine whether or not people have been exposed to higher levels of phthalates than levels found in the general population. These data will also help scientists plan and conduct research on phthalate exposure and health effects."

In summary, the mere presence of chemicals in the body does not imply it causes harm or elicits any biologically significant effect. Studies should take into account other factors including route and length of exposure, exposure effects, and route/rate of elimination.

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[1] *Third National Report on Human Exposure to Environmental Chemicals, U.S. Centers for Disease Control and Prevention, January 2003. http://www.cdc.gov/exposurereport/pdf/thirdreport.pdf*

Q: Does exposure to phthalates necessarily mean they are toxic?

A: Toxicology is based on the assertion that the dose makes the poison. Therefore, anything can be toxic at high enough exposure levels. In order for a substance to be proven toxic, a direct and causal relationship must be shown.

Some studies have shown exposure to certain phthalates causes reproductive effects in rodents. However, the metabolism of phthalates and the developing reproductive system in the rat is different from that of humans. Therefore, while these studies may be useful for suggesting what sorts of toxicity to look for, they do not indicate that it will pose any risk for humans. In addition, toxicity studies on laboratory rats are designed to show an effect, using doses high enough to elicit an effect. These doses often are much, much higher than what people are exposed to from everyday use of these chemicals.

For example, in their 2001 report to the Consumer Product Safety Commission, chairman of the DINP Chronic Hazard Advisory Panel (CHAP), Kenneth Brogan, reported that "although studies in rats indicate that DINP is a teratogen and reproductive toxicant, the risk to reproductive and development processes in humans due to DINP exposure is extremely low or non-existent." [2]

In addition, the CDC's 3rd biomonitoring report states that, "several phthalates produce testicular injury, liver injury, liver cancer, and teratogenicity in rodent studies, but these effects either have not been demonstrated when tested in non-human primates or people or have not been investigated." The report also cites the difference in absorption rates between rodents and humans. "For example, blood levels of phthalate monoesters can be higher in rodents than in non-human primates that are given equivalent doses due to the greater absorption in rodents."[3]

Note that level of exposure determines toxicity, not just any exposure. According to the safe exposure levels identified in the CHAP's report on DINP, if you took water and saturated it with DINP, an infant would have to drink more than 41,500 gallons every day to exceed this established safe DINP exposure limit. Infants from 3 months to 12 months spend a total of less than 10 minutes per day mouthing objects. The CHAP concluded that a baby would have to suck more than 10 times longer every day before he or she could consume enough DINP to have any potential for adverse effects [2]

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[2] Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Disononyl Phhtalates (DINP); June 2001

[3] *Third National Report on Human Exposure to Environmental Chemicals, U.S. Centers for Disease Control and Prevention, January 2003. http://www.cdc.gov/exposurereport/pdf/thirdreport.pdf*

Stevenson, Todd

From: Little Lark_Christy [christy@alittlelark.com]
Sent: Thursday, January 08, 2009 4:49 PM
To: Phthalates Project
Subject: Section 108: Phthalates in Children's Products - screen printing inks
Attachments: Heavy Metals and Phthalates 07-10-08.doc; ATT00001.txt

Hello and thank you in advance for taking the time to read my question and concern regarding Section 108 of the CPSIA..... primarily the issue of screen printing ink that contains phthalates.

I am a mother of two boys and also run a business from my home screen printing children's 100% cotton apparel, and many of my items are GOT certified organic cotton and colored with azo free dyes. Although I have recently switched all the ink I use over to PVC free ink, I do still have some older inventory in stock from early printing with plastisol inks. I am concerned that with this new law in place that I may no longer be able to sell this inventory..... even though, in my mind, the plastisol ink serves no hazards to a child who is wearing a shirt. A t-shirt is not a toy, nor is something that children put in their mouths. The only thing that actually makes contact with the child's skin is the cotton from the inside of the shirt.

Below is an attached letter that was sent to me by Union Inks Company, Inc. regarding my concerns of wether plastisol inks where within compliance with CPSIA. I would love to hear your comments based on the written contents of that letter.

I am a very small, but fast growing business and just now starting to make money. I need to know from you that I will be within compliance with the CPSIA if I attain all the required certification of compliance from the clothing manufacturers and the ink companies, since these are the only materials I use in my products. It would be too costly and redundant for me to have these articles tested again and could force me to stop operating my business.... especially for something I see as no threat to children, not to mention my own two boys.

Thanks again for reading my comments and I look forward to hearing back from someone in regards to my questions above.

All the best,

christy nyboer
owner + designer
little lark
www.alittlelark.com
503.358.1131

Stevenson, Todd

From: Erica Hamblen [erica_hamblen@yahoo.com]
Sent: Friday, January 09, 2009 10:21 AM
To: Phthalates Project
Subject: Passing the buck

Another example of the government penalizing retailers instead of manufacturers. Why on earth would you pass such a restrictive law regarding the testing of toys and children's clothing for lead and phthalates which would have such an impact on a very necessary part of our economy?

The safety of materials changes from time to time but ultimately the responsibility must reside with the manufacturers who selected these materials for their goods. It is they who should bear the responsibility of testing NOT retailers. These goods you seek to target are just too broad in scope and any law you pass will only result in yet another law on the books which cannot be enforced. How has it come to pass the bureaucracy has now come to rule our country instead of common sense?

As a citizen I strongly urge the commission to please start thinking instead of reacting and pass a law which makes sense! Not this convoluted mess you are attempting to enact by February 2009 which will only penalize second-hand retailers and Americans.

30

Stevenson, Todd

From: J Patrick Harmon [patrick.harmon@basf.com]
Sent: Friday, January 09, 2009 2:56 PM
To: Phthalates Project
Cc: J Patrick Harmon
Subject: Section 108: Phthalates in Children's Products - comments on Hexamoll(r) DINCH
Attachments: Hexamoll DINCH CPSIA Comments 1-9-09_001.PDF; CPSIA Hexamoll DINCH attachments.txt

Please find in the attachments our comments on the BASF plasticizer Hexamoll(r) DINCH to support the CPSC review of the use of phthalates and other plasticizers in children's products. For further information I can be contacted by email or phone as noted below. Supporting documents are included in the "zip" file.

(See attached file: Hexamoll DINCH CPSIA Comments 1-9-09_001.PDF)(See attached file: CPSIA Hexamoll DINCH attachments.zip)

J Patrick Harmon, Ph.D.
Industry Manager Oxo Alcohols and Plasticizers

Phone: 1-713-759-3087
Mobile: 1-281-413-4211
E-mail: patrick.harmon@basf.com
Postal Address:
BASF Corporation
1111 Bagby Street
Houston, TX 77002
USA

BASF - The Chemical Company

Stevenson, Todd

From: J Patrick Harmon [patrick.harmon@basf.com]
Sent: Monday, January 12, 2009 5:42 PM
To: Phthalates Project
Cc: J Patrick Harmon
Subject: Section 108: Phthalates in Children's Products - comments on DPHP

Categories: Technical comment

BASF Corporation, the North American affiliate of BASF SE, headquartered in Ludwigshafen, Germany, would like to submit brief comments on the product Palatinol® DPHP, dipropylheptyl phthalate, as part of the CPSC review under Section 108 of the Consumer Product Safety Improvement Act.

Dipropylheptyl phthalate (CAS# 53306-54-0, DPHP) is a type of phthalate ester that is used primarily as a plasticizer for flexible PVC applications. It was developed for use in applications such as automotive, roofing, pond liners, wire and cable insulation, and other construction products as well as some plastic consumer items. BASF does not promote its use in toys and childcare articles and believes it would be unlikely to find DPHP in these products. Typical concentrations in PVC formulations range from 10 - 40%. BASF currently produces the raw materials (phthalic anhydride and propylheptanol) and DPHP in Pasadena, Texas, and Ludwigshafen, Germany.

The toxicological properties of the product have been reviewed by third parties; for example, it was part of the High Molecular Weight Phthalate Esters (HMWPE) category for the 2004 OECD SIDS Initial Assessment Profile.
The conclusion of this review was that "chemicals in this category are currently of low priority for further work because of their low hazard profile." The report may be found at http://cs3-hq.oecd.org/scripts/hpv/.

Should you require additional information on DPHP as part of your review on phthalates in children's product, you may reach me using the contact information below.

Best regards,

Patrick Harmon

J Patrick Harmon, Ph.D.
Industry Manager Oxo Alcohols and Plasticizers

Phone: 1-713-759-3087
Mobile: 1-281-413-4211
E-mail: patrick.harmon@basf.com
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BASF - The Chemical Company

BASF
The Chemical Company

January 9, 2009

Office of the Secretary
Consumer Product Safety Commission
Room 502
4330 East-West Highway
Bethesda, MD 20814

By email to phthalates-info@cpsc.gov and via U.S. Mail

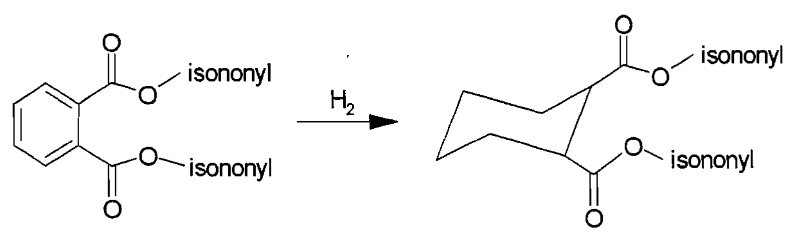
Section 108: Phthalates in Children's Products

Comments on a BASF phthalate alternative, Hexamoll® DINCH

In response to the CPSC request for comments and information on phthalates and phthalate alternatives, BASF Corporation[1] is submitting this information on Hexamoll® DINCH, diisononyl 1,2 cyclohexane dicarboxylate (US CAS# 474919-59-0, EU CAS# 166412-78-8). The comments are presented in the order listed in the CPSC request for comments.

1. Product and technical characteristics

   Hexamoll® DINCH (afterwards referred to as "DINCH") is produced by selective hydrogenation of diisononyl phthalate (DINP, CAS# 28553-12-0); the product is 90 ±10% of the *cis*-isomer and 10 ±10% of the *trans*-isomer. The product is produced in a 100,000 metric ton per year plant at the BASF SE site in Ludwigshafen, Germany.



DINP **DINCH**

   The current sales specification limit for residual phthalate content is 0.01% (100 ppm); the typical content in the current product is around 0.005% (50 ppm).[2]

   The product is used primarily as a plasticizer for flexible vinyl products. As shown in the attached report, it may be used as an effective replacement for general purpose plasticizers

[1] BASF Corporation is the North American affiliate of BASF SE, headquartered in Ludwigshafen, Germany.
[2] BASF SE, Hexamoll® DINCH Technical Leaflet, January 2008 (attached).

BASF Corporation
1111 Bagby Street, Suite 2600
Houston, TX 77002
Tel: 713-759-3000
www.basf.com/usa

such as DEHP and DINP in most applications, particularly those where higher exposure is possible.[3]

2. Use

DINCH was introduced to the global market in 2002 as an alternative plasticizer for sensitive exposure applications such as toys, food packaging, and medical devices. To our knowledge it currently makes up over 50% of the global consumption of plasticizers in children's toys. While its largest market is for toy production, it also is being used to make other children's products as well as additional consumer products and sports equipment such as exercise mats, fitness balls, and various other inflatable items. It is now used in some medical devices in Europe and in food packaging materials in Europe and Asia. Typical concentrations in PVC formulations range from 10 – 40%, as is also typical for other plasticizers in flexible vinyl.

3. Reference materials and testing

Samples of DINCH for use as a reference material may be obtained by contacting BASF Corporation.

The DINCH content of vinyl products may be determined by extraction and analysis similar to ASTM D7083-04[4] or the procedure from the CPSC website.[5]

4. Toxicity

DINCH has been thoroughly tested in order to ensure the safety of the product for its intended uses. The total cost for toxicological testing for DINCH is now over 5 million Euros. The studies, which followed the most recent OECD or EU guidelines, have clearly shown no relevant hazards for the following endpoints: cancer, testicular toxicity, impairment of fertility, developmental toxicity, teratogenicity, and endocrine action. No environmental hazards were observed, and the product does not accumulate in the body.[6]

Three independent reviews (attached) by government agencies in Europe and Australia have recently been completed that provide useful summaries of these tests. These reviews are:

European Food Safety Authority (EFSA). The EFSA Journal (2006) 395 to 401, p. 1 – 8, 12th list of substances for food contact materials. The review established a Tolerable Daily Intake (TDI) of 1 mg/kg bw/day with no specific migration limit for food use. http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1178620770921.htm.

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[3] BASF, Comparison of Hexamoll® DINCH to Palatinol® AH (DEHP, DOP) and Palatinol® N (DINP), August 2008.
[4] ASTM D7083-04, *Standard Practice for Determination of Monomeric Plasticizers in Polyvinyl Chloride (PVC) by Gas Chromatography*.
[5] See the following link: www.cpsc.gov/about/cpsia/phthalate_test_method.pdf.
[6] The toxicological studies were carried out only on the BASF product Hexamoll® DINCH; the results may not necessarily apply to other similar products.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS). Full Public Report, 1,2-Cyclohexanedicarboxylic acid, 1,2-diisononyl ester ('Hexamoll® DINCH'), File No. STD/1259, August 2008. The review established a Tolerable Daily Intake (TDI) of 0.40 mg/kg bw/day.
http://www.nicnas.gov.au/publications/car/new/std/stdsummr/std1000sr/std1259.asp.

Scientific Committee on Emerging and Newly Indentified Risks (SCENIHR). Opinion on the Safety of Medical Devices Containing DEHP-Plasticized PVC or Other Plasticizers on Neonates and Other Groups Possibly at Risk, 6 February 2008, p. 41 – 44 (alternative plasticizers discussion) and 80 – 82 (DINCH-specific discussion).
http://ec.europa.eu/health/ph_risk/risk_en.htm.

Additional details on these studies are available from BASF upon request.

5. Migration and exposure

Plastic Toys

Migration of DINCH from toys into simulated saliva is shown in the following table:[7]

[redacted]						
DINCH	0.35	180	63	7.9	107	13,587

[1] European CSTEE model, mouthing for 180 minutes.
[2] CSTEE model, body weight of 8 kg.
[3] NOAEL taken from the published EFSA opinion.

Using the conservative NOAEL from the EFSA opinion and the equally conservative estimated mouthing time of 180 min from the European CSTEE opinion, the expected exposure to DINCH is far below any level of concern. When using the more realistic mouthing times determined in the 2001 mouthing study by CPSC,[8] the margin of safety would be even greater.

Other migration studies

The migration of DINCH into various foodstuffs is described in the EFSA and NICNAS opinions. The expected exposure from food contact was found to be below the established TDI for the intended applications.

[7] Data taken from LGA Nuernburg, Germany, from a migration study contracted by a customer of BASF SE. Presented at Plasticizers 2008, 29 – 30 January 2008, Dr. Rainer Otter, BASF SE, "Case study: Plasticizers for human contact applications," Slide 16 (attached file, Otter 1011_N_iss_679_2351.pdf).
[8] Kiss, C.T., US CPSC, A Mouthing Observation Study of Children Under 6 Years of Age, November 2001.

The comparison of the migration of DINCH versus DEHP into enteral feeding solutions also has been determined in a study by the Fraunhofer Institute (attached).[9] The migration of DINCH was found to be 8-fold less than with DEHP and significantly less than the TDI established by EFSA.[10]

6. Other information

DINCH has been determined to have the highest eco-efficiency in a comparison of the top five non-phthalate plasticizers on the market today based on the results of a BASF eco-efficiency analysis (attached).[11] This analysis was verified by the impartial German organization TÜV Rheinland. BASF analyzed the eco-efficiency of non-phthalate plasticizers for three everyday product groups: children's balls, tubing for medical devices, and garden hoses. The eco-efficiency analysis assesses both the ecological properties and costs of a product over its complete life cycle from manufacture to end of life.

For further information please contact me at 713-759-3087 or by email at patrick.harmon@basf.com.

Best regards,

Patrick Harmon
Industry Manager Oxo Alcohols and Plasticizers

[9] Welle, F., Wolz, G., and Franz, R., Migration of plasticizers from PVC tubes into enteral feeding solutions, *Pharma International*, 3, 2005, p. 17 – 21.
[10] See Slide 20 in the presentation references in Note 7 above.
[11] BASF, Label Eco-Efficiency Analysis Hexamoll® DINCH, 10 May 2008. The presentation describes the analysis and includes a copy of the certificate. It may be found at
http://www.basf.com/group/corporate/en_GB/content/sustainability/eco-efficiency-analysis/label.

Migration von Weichmachern aus PVC Schläuchen in enterale Nahrungslösungen

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Einführung

PVC wird für vielfältige medizinische Anwendungen eingesetzt. Die funktionalen Eigenschaften von PVC eignen sich in hohem Maße für eine Vielfalt von medizinischen Produkten. Das von Natur aus spröde und harte PVC wird dabei mit Substanzen wie Di-(2-ethylhexyl)phthalat (DEHP) weichgemacht. Derartige Weichmacher haben prinzipiell ein niedriges Molekulargewicht, da sie innerhalb der molekularen Struktur des Polymers beweglich sein müssen, um die gewünschten Effekte zu erzeugen. Als unabwendbare Konsequenz daraus resultiert eine signifikante Migration des Weichmachers in Kontaktmedien. Voraussetzung dafür ist jedoch, dass die Löslichkeit des Weichmachers in den Kontaktmedien hoch genug ist. Im Falle von enteralen Nahrungslösungen, die normalerweise über einen gewissen Fettgehalt verfügen, kann diese Migration von Weichmachern aus den Ernährungssets zu einer beträchtlichen Weichmacherbelastung des Patienten führen, da in der Regel die Überführungsschläuche und manchmal zusätzlich noch die Beutel aus weichgemachtem PVC bestehen. Daher muss der Einsatz von Weichmachern bei der medizinischen Versorgung von Patienten berücksichtigt werden. Insbesondere bei Frühgeborenen, die enteral ernährt werden müssen, kann die Belastung mit Weichmachern bezogen auf das Körpergewicht besonders hoch ausfallen.

Der derzeit in medizinischen Anwendungen noch am häufigsten eingesetzte Weichmacher, das Di-(2-ethylhexyl)phthalat (DEHP), ist aufgrund seiner fruchtbarkeitsbeeinflussenden und fruchtschädigenden Wirkung im Tierversuch als toxisch gekennzeichnet. Das europäische wissenschaftliche Komitee für Nahrungsmittelsicherheit (Scientific Committee on Food SCF) hat für DEHP eine maximal zulässige, tägliche Dosis (TDI) von 50 µg pro kg Körpergewicht festgelegt [1]. Das wissenschaftliche Komitee für Medizinprodukte und medizinische Geräte (Scientific Committee on Medical Products and Medical Devices (SCMPMD)) wollte sich aufgrund der Daten nicht auf eine höchstzulässige tägliche Zufuhrmenge festlegen, sondern betont stattdessen die Abwägung zwischen erzielbarem Nutzen und möglichen Risiken[2]. Gleichwohl wird in der Veröffentlichung darauf hingewiesen, dass einige Gruppen einem höheren Risiko durch die Behandlung ausgesetzt sein können. Das SCMPMD forderte dringend dazu auf, die Datenlage bei möglichen Alternativen zu verbessern.

Vor dem Hintergrund der anhaltenden Diskussion um DEHP rücken Alternativen ins Blickfeld des öffentlichen Interesses. Besonders interessant sind solche Alternativen,

Migration of plasticizers from PVC tubes into enteral feeding solutions

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Fraunhofer Institute for Process Engineering and Packaging IVV, Giggenhauser Straße 35, 85354 Freising, Germany

Introduction

PVC is used for a wide range of medical applications and has excellent functional properties for many medical products. PVC is by nature hard and brittle and is made softer using substances such as di-(2-ethylhexyl)phthalate (DEHP). These plasticizers must have a low molecular weight in order to be mobile within the molecular structure of the polymer and so induce the desired effects. An unavoidable consequence of this is significant migration of the plasticizer into the contact media. This migration occurs if the solubility of the plasticizer in the contact media is sufficiently high. In the case of enteral feeding solutions, which normally have a certain fat content, this migration of plasticizers from the feeding equipment (sets) can lead to considerable amounts of plasticizer entering the patient's body. This is because in general the transfer tubes and sometimes also the bags themselves are made of plasticized PVC. This is especially important for premature babies who have to undergo enteral feeding. In such babies, the amount of plasticizer taken up, relative to the body weight, can be particularly high.

The most common plasticizer currently used for medical applications is di-(2-ethylhexyl)phthalate (DEHP). In animal experiments this chemical has been shown to impair fertility and cause malformations and has hence been labeled as toxic. The EU Scientific Committee on Food (SCF) has laid down a maximum tolerable daily intake (TDI) for DEHP of 50 µg per kg body weight[1]. On the basis of the data, the EU Scientific Committee on Medical Products and Medical Devices (SCMPMD) did not want to set a maximum tolerable daily intake but instead stresses the balance between realizable benefits and possible risks[2]. It was however pointed out in the publication that some groups could be subjected to a higher risk as a result of the treatment. The SCMPMD demanded that detailed information about possible alternative materials should be urgently acquired.

Against the background of this ongoing discussion about DEHP, alternative materials have come into the public interest. Of particular interest are alternative materials that are technically equivalent and which have more favorable toxicological properties and/or significantly lower migration, so lowering the exposure of patients to the materials. Alternative materials such as for example acetyl tributyl citrate (ATBC), di-(2-ethylhexyl) adipate (DEHA; also known as di-octyl adipate (DOA)) and tri-(2-ethylhexyl) trimellitate (TEHTM) are used occasionally. Another substance was recently proposed as an alternative to DEHP: Di-(isononyl)-cyclohexane-1,2-dicarboxylate welche technisch gleichwertig sind und toxikologisch günstigere Eigenschaften vorweisen können und/oder eine signifikant geringere Migration aufweisen und somit die Exposition des Patienten verringern. Alternativen wie zum Beispiel Acetyltributylcitrat (ATBC), Di-(2-ethylhexl)adipat (DEHA; Synonym: DOA) oder Tri-(2-ethylhexyl)trimelitat (TEHTM) werden vereinzelt eingesetzt. Kürzlich wurde eine weitere Substanz als Alternative zu DEHP vorgeschlagen: Di-(isononyl)-cyclohexan-1,2-dicarboxylat (DINCH). Diese Alternative weist im Vergleich zu DEHP günstigere toxikologische Eigenschaften auf. Während für DEHP zum Beispiel wegen Hodentoxizität und entwicklungsschädigender Wirkung eine Dosis ohne adversen Effekt (NOAEL: No observed adverse effect level) von 4.8 mg pro kg Körpergewicht und Tag festgesetzt wurde[3], zeigten entsprechende Studien für DINCH bei Dosierungen von 1000 mg pro kg Körpergewicht und Tag und mehr keine adversen Effekte[4]. DINCH wurde überdies nicht nur an Nagern (Ratte), sondern bezüglich möglicher fruchtschädigender Eigenschaften auch am Kaninchen geprüft. Auch hier traten selbst bei der höchsten geprüften Dosierung von 1000 mg pro kg Körpergewicht keine fruchtschädigenden Wirkungen auf. DINCH wurde kürzlich vom deutschen Bundesinstitut für Risikobewertung (BfR) mit einem Migrationsgrenzwert von 5 mg pro kg Lebensmittel für Materialen im Kontakt mit Lebensmittel zugelassen[5]. Bei DEHA liegt der spezifische Migrationsgrenzwert in der EU bei 18 mg pro kg Lebensmittel (2002/72/EC). Die anderen beiden Alternativen sind bisher nicht in der 2002/72/EC genannt. ATBC ist z.B. in Deutschland ebenfalls in der Empfehlung I der Kunststoffkommission genannt, allerdings noch mit einer Begrenzung des Gehaltes im Fertigprodukt und nicht wie DINCH mit einem spezifischen Migrationsgrenzwert. TEHTM ist für den Lebensmittelkontakt nach den uns vorliegenden Informationen nicht zugelassen.

Ein wichtiger, bisher fehlender Parameter für die Bewertung von DINCH im Vergleich zu DEHP oder anderen Alternativen bei der klinischen Ernährung, war dessen Migrationsverhalten bei Kontakt mit realen Ernährungslösungen. Ziel dieser Studie war daher die praxisnahe Bestimmung der Migration von DINCH im Vergleich zum derzeitigen Standard DEHP, aber auch zu anderen als Alternativen diskutierten Weichmachern wie TEHTM und ATBC aus PVC Schläuchen in enterale Nahrungslösungen unter realen Anwendungsbedingungen.

Vorgehensweise und Materialien

Handelsübliche Ernährungslösungen für Erwachsene oder für Neugeborene wurden mit handelsüblichen Überleitgeräten (Sets), welche mit unterschiedlichen Weichmachern gefertigt wurden getestet. Bis auf das Set mit DINCH als Weichmacher, waren zum damaligen Zeitpunkt alle Sets kommerziell erhältlich. Die Sets wurden jeweils mit den empfohlenen Pumpen geprüft, so dass auch die mechanische Beanspruchung den realen Bedingungen entsprach. Die Gesamtdauer der Experimente betrug jeweils 24 Stunden. Dies entspricht der empfohlenen, maximalen Nutzungsdauer eines einzelnen Überleit-

(DINCH). This substance has more favorable toxicological properties than DEHP. For example, due to its testicular toxicity and teratogenicity, DEHP has an NOAEL (No Observed Adverse Effect Level) of 4.8 mg per kg body weight per day[3]. In contrast, no adverse effects were found in respective studies on DINCH at doses of 1000 mg and more per kg body weight per day[4]. DINCH was not only tested on rodents (rats), but was also tested on rabbits for possible adverse reproductive effects. Even at the highest tested doses of 1000 mg per kg body weight, no adverse reproductive effects were observed. DINCH was recently approved by the German Institute for Risk Assessment (Bundesinstitut für Risikobewertung (BfR)) with a migration limit of 5 mg per kg food for materials in contact with foods[5]. For DEHA the specific migration limit in the EU is 18 mg per kg food (2002/72/EC). The two other alternative materials have up until now not been mentioned in 2002/72/EC. ATBC is, for example, in Germany also mentioned in Recommendation I of the Plastics Committee. However, a limit is set on the concentration in the finished product rather than a specific migration limit as is the case for DINCH. According to the information available to us, TEHTM is not approved for food contact applications.

In order to compare the use of DINCH with DEHP and other alternative materials in equipment for clinical feeding, information about the migration behavior of DINCH into real feeding solutions is necessary. This information has been hitherto unavailable. The objective of this study was therefore to determine the migration of DINCH under real application conditions and to compare the results with the same experiments carried out using standard DEHP. Comparison was also made with the other alternative plasticizers (TEHTM and ATBC).

Experimental procedure and materials

Commercially available feeding solutions for adults and for new born babies were tested using commercially available feeding sets made with different plasticizers. Except for the feeding set with DINCH as the plasticizer, all the other feeding sets were commercially available at the time the experiments were undertaken. Each of the feeding sets was tested with the recommended pump, meaning that the mechanical loads corresponded to real conditions. Each experiment was carried out for 24 hours. This corresponds to the recommended maximum period of use of an individual feeding set. For the experiments, the feeding solutions were transferred to the feeding sets in accordance with the information on the bottles. Each feeding set was tested with the recommended pump set at standard flow rates. The experiments were carried out at room temperature. After passing through the feeding set, samples were collected in different fractions and then quantitatively analyzed for the concentration of plasticizer. The concentrations of plasticizer in the individual fractions were added to give the total quantity of plasticizer taken up by patients.

The following materials and feeding solutions were used for the experiments:

geräts. Für die Tests wurden die Ernährungslösungen gemäß den Angaben auf den Flaschen in die Überleitgeräte überführt. Jedes Set wurde mit der empfohlenen Pumpe und mit üblichen Tropfgeschwindigkeiten geprüft. Die Anwendung erfolgte bei Raumtemperatur. Nach dem Passieren des Überleitgeräts wurden Proben fraktioniert aufgefangen und anschließend quantitativ auf den Gehalt an Weichmachern untersucht. Die Konzentrationen an Weichmachern pro Fraktion addieren sich auf zur Gesamtaufnahmemenge an Weichmachern, die den Patienten während der Applikation verabreicht würde.
Folgende Materialien und Ernährungslösungen wurden verwendet:

- Enterale Ernährungslösung A: Für Erwachsene, Gebindegröße 500 ml, 5.8% Fett pro 100 ml, empfohlene Anwendung mit 38 ml h^{-1}
- Enterale Ernährungslösung B: Für Kinder, Gebindegröße 60 ml, 4.4% Fett pro 100 ml, empfohlene Anwendung mit 5 ml h^{-1}
- Enterale Ernährungslösung C: Für Erwachsene, Gebindegröße 500 ml, 10% Fett pro 100 ml, empfohlene Anwendung mit 38 ml h^{-1}
- Set 1: kommerziell erhältliches Überleitungsset mit DEHP-weichgemachten PVC Schläuchen (DEHP Gehalt 41.5%) und weichmacherfreiem EVA Beutel.
- Set 2: kommerziell erhältliches Überleitungsset mit DEHP-weichgemachten PVC Schläuchen (DEHP Gehalt 48.9%) und weichmacherfreiem EVA Beutel.
- Set 3: Pilotanwendung von DINCH-weichgemachten PVC Schläuchen (DINCH Gehalt 29.6%) und weichmacherfreiem EVA Beutel.
- Set 4: kommerziell erhältliches Überleitungsset mit TEHTM-weichgemachten PVC Schläuchen (TEHTM Gehalt 37.1%) und weichmacherfreiem EVA Beutel.
- Set 5: kommerziell erhältliches Überleitungsset mit DEHP-weichgemachten PVC Schläuchen (DEHP Gehalt 48.9%) und PVC Beutel.
- Set 6: kommerziell erhältliches Überleitungsset mit ATBC-weichgemachten PVC Schläuchen (ATBC Gehalt 28.0%) und weichmacherfreiem EVA Beutel.

Ergebnisse und Diskussion

Die Abbildungen 1 bis 4 zeigen die kumulierten Migrationen der verschiedenen Weichmacher in die einzelnen Ernährungslösungen. Aus den Kurven ist ersichtlich, dass jeweils das Fließgleichgewicht bereits nach relativ kurzer Zeit erreicht ist. Die Weichmacherabgabe ist damit über die Anwendungszeit nahezu konstant. Eine Ausnahme bildete das ATBC System, wo bei längeren Anwendungszeiten wieder geringere Migrationen messbar waren. ATBC erreichte jedoch im Vergleich zu den anderen Weichmachern extrem hohe Migrationswerte, so dass die daraus resultierende merkliche Verringerung der Konzentration von ATBC im Schlauch selbst zu dem beobachteten Effekt führt.
Als Ergebnis zeigt sich, dass im Falle des DINCH Systems die Migration deutlich geringer ist als bei DEHP. TEHTM zeigt aufgrund seines höheren Molekulargewichts und aufgrund seiner sehr geringen Löslichkeit in den Ernäh-

- Enteral feeding solution A: For adults, container size 500 ml, 5.8% fat per 100 ml, recommended application rate 38 ml h^{-1}
- Enteral feeding solution B: For children, container size 60 ml, 4.4% fat per 100 ml, recommended application rate 5 ml h^{-1}
- Enteral feeding solution C: For adults, container size 500 ml, 10% fat per 100 ml, recommended application rate 38 ml h^{-1}
- Feeding set 1: Commercially available feeding set with DEHP plasticized PVC tubing (DEHP content 41.5%) and plasticizer-free EVA bag.
- Feeding set 2: Commercially available feeding set with DEHP plasticized PVC tubing (DEHP content 48.9%) and plasticizer-free EVA bag.
- Feeding set 3: Pilot application of DINCH plasticized PVC tubing (DINCH content 29.6%) and plasticizer-free EVA bag.
- Feeding set 4: Commercially available feeding set with TEHTM plasticized PVC tubing (TEHTM content 37.1%) and plasticizer-free EVA bag.
- Feeding set 5: Commercially available feeding set with DEHP plasticized PVC tubing (DEHP content 48.9%) and PVC bag.
- Feeding set 6: Commercially available feeding set with ATBC plasticized PVC tubing (ATBC content 28.0%) and plasticizer-free EVA bag.

Results and discussion

Figures 1 to 4 show the cumulative migration of the various plasticizers into the individual feeding solutions. It can be seen from the curves that in each case a flow equilibrium is reached after a relatively short period of time. The release of plasticizer is hence virtually constant throughout the application time. The ATBC system is an exception and in this case lower migration was measured at long application times. Compared to the other plasticizers, ATBC did however show extremely high migration values, meaning that the marked reduction of the ATBC concentration in the tube itself resulted in the observed effect.
The results show that migration in the DINCH system is considerably lower than for DEHP. TEHTM showed even lower migration values due to its higher molecular weight and very low solubility in the feeding solutions. In the TEHTM system it must be taken into account that DEHP is a side-product here. Although the cumulative migration of TEHTM into feed solution B (4.4% fat per 100 ml) was very low (1.6 µg), at the same time ca. 67µg DEHP passed from the feeding set under test into the same feeding solution. This shows that in the TEHTM system the migration of DEHP cannot be neglected. ATBC showed by far the highest migration of plasticizer. Despite the lower concentration of the plasticizer in the polymer, this value was at least an order of magnitude greater than the migration of DEHP. This high migration can be put down to the very high solubility of ATBC in the feeding solutions.
Figure 5 compares the migration of DEHP for DEHP-free EVA bags and for PVC bags plasticized with DEHP. As

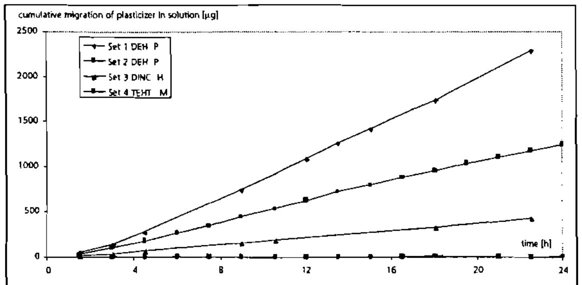

Abbildung 1: Kumulierte Migration der Weichmacher in Nahrungslösung A (5.8% Fett) unter realen Applikationsbedingungen (Gesamtdauer 24, Raumtemperatur, Förderrate 38 ml h-1), fehlende Werte wurden extrapoliert

Figure 1: Cumulative migration of plasticizer into feeding solution A (5.8% fat) under real application conditions (total duration of the experiments 24, room temperature, feed rate 38 ml h-1), missing values were extrapolated

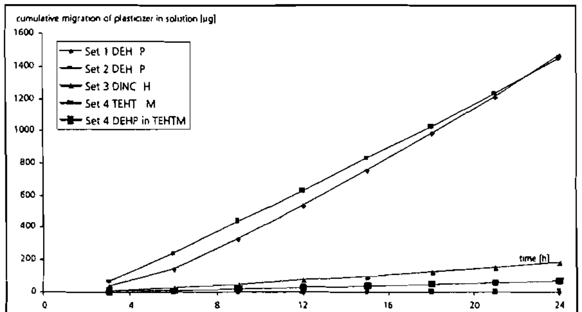

Abbildung 2: Kumulierte Migration der Weichmacher in Nahrungslösung B (4.4% Fett) unter realen Applikationsbedingungen (Gesamtdauer 24, Raumtemperatur, Förderrate 5 ml h-1)

Figure 2: Cumulative migration of plasticizers into feeding solution B (4.4% fat) under real application conditions (total duration of the experiments 24 h, room temperature, feed rate 5 ml h-1)

rungslösungen noch geringere Migrationswerte. Beim TEHTM System ist jedoch zu berücksichtigen, dass hier DEHP als Nebenprodukt enthalten ist. Die kumulierte Migration an TEHTM in Ernährungslösung B (4.4% Fett pro 100 ml) war zwar mit 1.6 µg sehr gering, gleichzeitig gingen bei dem untersuchten Überleitungsset ca. 67 µg DEHP in dieselbe Ernährungslösung über. Dies zeigt, dass beim TEHTM System die Migration von DEHP nicht vernachlässigt werden kann. Mit Abstand die höchsten Weichmacher-Migrationswerte zeigte ATBC. Sie lag trotz geringerem Anteil des Weichmachers im Polymer um mindestens eine Größenordung über der Migration von DEHP. Diese hohe Migration von ATBC ist auf die sehr gute Löslichkeit von ATBC in den Ernährungslösungen zurückzuführen.

Abbildung 5 zeigt die Migration von DEHP bei DEHP-freien EVA Beuteln im Vergleich zu PVC-Beuteln mit DEHP als Weichmacher. Erwartungsgemäß erhöht sich die Migration, wenn auch der Vorratsbeutel ebenfalls DEHP enthält. Nach den Ergebnissen dieser Studie liegt die Erhöhung konstant bei etwa 20% über der Migration bei Verwendung von DEHP-freien EVA Beuteln.

Zusammenfassend lässt sich sagen, dass Weichmacher in erheblichem Maße in die Ernährungslösungen übergehen können. Andererseits sind Weichmacher jedoch für die

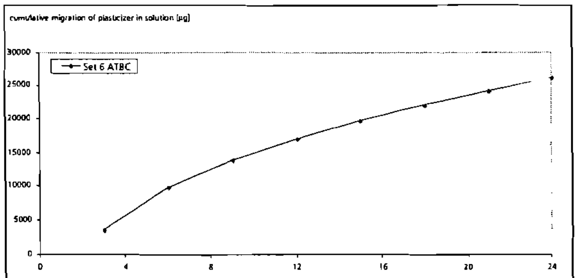

Abbildung 3: Kumulierte Migration von ATBC in Nahrungslösung B (4.4% Fett) aus Set 6 unter realen Applikationsbedingungen (Gesamtdauer 24, Raumtemperatur, Förderrate 5 ml h-1), geänderte Skalierung!

Figure 3: Cumulative migration of ATBC into feeding solution B (4.4% fat) from set 6 under real application conditions (total duration of the experiment 24 h, room temperature, feed rate 5 ml h-1) (please note the change of scale on the y-axis!)

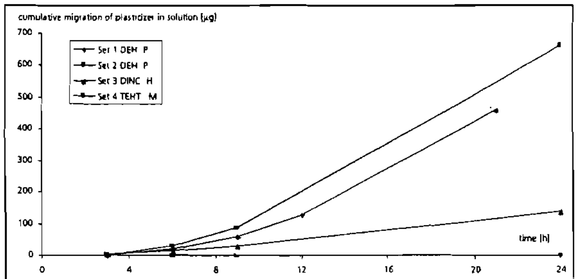

Abbildung 4: Kumulierte Migration der Weichmacher in Nahrungslösung C (10% Fett) unter realen Applikationsbedingungen (Gesamtdauer 24, Raumtemperatur, Förderrate 38 ml h-1), fehlende Werte wurden extrapoliert

Figure 4: Cumulative migration of plasticizer into feeding solution C (10% fat) under real application conditions (total duration of the experiments 24 h, room temperature, feed rate 38 ml h-1), missing values were extrapolated

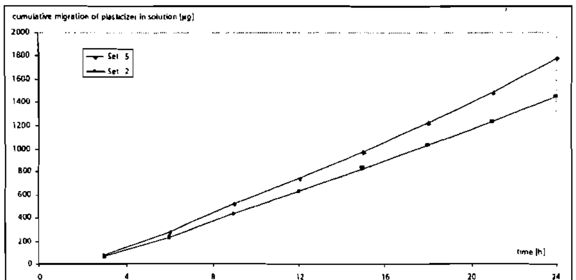

Abbildung 5: Kumulierte Migration von DEHP in Nahrungslösung B (4.4% Fett) aus Set 2 (weichmacherfreier EVA Beutel) und Set 5 (PVC Beutel enthielt ebenfalls DEHP als Weichmacher) unter realen Applikationsbedingungen (Gesamtdauer 24, Raumtemperatur, Förderrate 5 ml h-1)

Figure 5: Cumulative migration of DEHP into feeding solution B (4.4% fat) from set 2 (plasticizer-free EVA bag) and set 5 (PVC bag contain DEHP as plasticizer) under real application conditions (total duration of the experiments 24 h, room temperature, feed rate 5 ml h-1)

expected, the migration increases when the stock solution bag also contains DEHP. According to the results of these studies, the increase is constant at about 20% greater than the migration when using DEHP-free EVA bags.

It can be concluded that considerable quantities of plasticizer can transfer into the feeding solutions. However, plasticizers are vital for the functional properties of the products. It is not possible to completely do without plafunktionalen Eigenschaften der Produkte entscheidend. Ein völliger Verzicht von Weichmachern ist nicht möglich. Die Konsequenz ist, dass auch der Übergang der Weichmacher in die Ernährungslösung nicht völlig verhindert werden kann. Entscheidend wird damit zwangsläufig das Ausmaß des Übergangs sowie das toxikologische Profil eines Weichmachers.

Die Expositionsberechung für DEHP im Vergleich zu DINCH für die in der Studie angewandten Bedingungen sieht folgendermaßen aus: Eine Person mit einem durchschnittlichen Körpergewicht von 60 kg würde einer Belastung durch DEHP von 0.024 mg pro kg Körpergewicht und Tag ausgesetzt sein. Beim alternativen DINCH ist die Belastung aufgrund der geringeren Migrationsrate mit 0.003 mg pro kg Körpergewicht und Tag geringer. Bei einem Neugeborenen mit 2 kg Körpergewicht entspräche dies 0.726 mg DEHP bzw. 0.094 mg DINCH pro kg Körpergewicht und Tag. Vergleicht man dies mit den spezifischen Migrationsgrenzwerten (SML) Lebensmittelkontaktmaterialien von 0.05 mg für DEHP bzw. 0.0083 mg pro kg Körpergewicht und Tag für DINCH, so ergibt sich für DINCH bei einer Person mit 60 kg Körpergewicht eine Exposition mit nur 0.036 SML Äquivalenten, wohingegen auch ein Neugeborenes nur im Bereich des gegenwärtig tolerierten SML exponiert wäre. Für DEHP ergeben sich entsprechend 0.48 SML Äquivalenten bei einem Erwachsenen mit 60 kg Körpergewicht und einer etwa 14.5-fachen Überschreitung des spezifischen Migrationsgrenzwerts bei einem Neugeborenen. Dies zeigt, wie dringlich die Suche und Entwicklung von Alternativen für den Weichmacher DEHP im Bereich der enteralen Ernährung ist.

Danksagung

Wir danken BASF AG, Ludwigshafen, Raumedic AG, Münchberg, und Nutricia Clinical, Schiphol, für das zur Verfügung gestellte Testmaterial und für die finanzielle Unterstützung dieser Arbeit.

Literatur

[1] European Commission DG SANCO D3: Doc. INT/SYNOPTIC DOCUMENT (04/2003) updated to 13 May 2003

[2] European Commission DG SANCO: Doc. SANCO/SCMPMD/2002/0010 Final - Opinion on Medical devices containing DEHP plasticised PVC; neonates and other groups possibly at risk from DEHP toxicity (adopted 26 September 2002)

[3] European Commission DG SANCO: Doc. C7/GF/csteeop/DEHP/080104 D(04) – Opinion on the results of a second risk assessment of DEHP Human health part (adopted by CSTEE 8. January 2004)

[4] Otter R. and Goth H., 2004, Hexamoll® DINCH – our response to the plasticiser challenge. Presentation at the Conference «Plasticiser 2004», Brussels, September 2004

[5] Recommendations of the German Plastics Commission of BfR, Berlin, Bundesgesundheitsblatt – Gesundheitsforschung – Gesundheitsschutz 2004 47:602-604 ■

sticizers and as a consequence the transfer of plasticizers into feed solutions cannot be fully prevented. The key issues are hence the extent of the migration and the toxicological properties of the plasticizers.

Calculation of the exposure to DEHP and DINCH under the conditions used in the experiments is carried out as follows: A person with an average body weight of 60 kg would be exposed to a DEHP concentration of 0.024 mg per kg body weight per day. For DINCH, the exposure of 0.003 mg per kg body weight per day is lower due to the lower migration rate. For a new born baby weighing 2 kg, the equivalent values are respectively 0.726 mg DEHP and 0.094 mg DINCH per kg body weight per day. If this is compared to the specific migration limits (SML) for food contact materials of 0.05 mg for DEHP and 0.0083 mg for DINCH per kg body weight per day, then exposure of a person weighing 60 kg to DINCH is only 0.036 SML equivalents, whereas even a new born baby would only be exposed in the range of the currently tolerated SML. For DEHP the corresponding value is 0.48 SML equivalents for an adult weighing 60 kg and about 14.5 SML equivalents for a new born baby. This highlights the urgency of the search for and development of alternative plasticizers to DEHP in the area of enteral feeding.

Acknowledgement

We would like to thank BASF AG (Ludwigshafen), Raumedic AG (Münchberg), and Nutricia Clinical (Schiphol) for funding this work and for making available the test materials.

Literature

[1] European Commission DG SANCO D3: Doc. INT/SYNOPTIC DOCUMENT (04/2003) updated to 13 May 2003

[2] European Commission DG SANCO: Doc. SANCO/SCMPMD/2002/0010 Final – Opinion on Medical devices containing DEHP plasticised PVC; neonates and other groups possibly at risk from DEHP toxicity (adopted 26 September 2002)

[3] European Commission DG SANCO: Doc. C7/GF/csteeop/DEHP/080104 D(04) - Opinion on the results of a second risk assessment of DEHP Human health part (adopted by CSTEE 8. January 2004)

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BASF
The Chemical Company

® = Registered trademark of BASF SE

Hexamoll® DINCH

**Plasticizer for PVC and other polar polymers.
This product can be used in applications that are particularly sensitive from the toxicological point of view.**

Chemical nature

1,2-Cyclohexanedicarboxylic acid, diisononyl ester

Molecular formula:	$C_{26}H_{48}O_4$	
CAS Number:	166412-78-8 474919-59-0	Europe and Asia USA
EC Nummer:	431-890-2	

Delivery specification

Property	Value	Unit	Test method DIN/ASTM
Dynamic viscosity* at 20 °C	44–60**	mPa·s	DIN 51562/D 445
Density* at 20 °C	0.944–0.954	g/cm^3	DIN 51757/D 4052
Platinum-cobalt colour	40 max.		DIN EN ISO 6271-2/ D 5386
Refractive index* n_D^{20}	1.460–1.466		DIN 51423/D 1045
Acid value	0.07 max.	mg KOH/g	DIN EN ISO 2114/ D 1045
Ester content	99.5 min.	% by area	by gaschromatography***
Water content	0.1 max.	% by weight	DIN 51777, Part 1/ E 203
Phthalate content	0.01 max.	%	UV-BASF
Metal content*			
Sb, As, Ba, Sn	1 max. each	ppm	ICP-MS
Cr, Pb, Hg, Se	1 max. each	ppm	ICP-MS
Cd	0.6 max.	ppm	ICP-MS

** These properties are not measured routinely.*
*** Calculated by multiplying the measured kinematic viscosity (DIN 51562) with the density.*
**** See page 3 for GC conditions. (General information on gas chromatography is given, e.g. in Lit [1])*

Properties

Hexamoll DINCH is a colourless, clear and practically anhydrous liquid with a hardly noticeable odour. It is soluble in the usual organic solvents and is miscible and compatible with all of the monomeric plasticizers commonly used in PVC. Hexamoll DINCH is almost insoluble in water.

Physical data

The following physical data were measured in the BASF SE laboratories. They do not represent any legally-binding guarantee of properties for our sales product.

Molar mass 424.7 g/mol

Pour point −54 °C (DIN ISO 3016)

Vapour pressure

T [°C]	P [hPa]
50	$1.3 \cdot 10^{-6}$
60	$5.5 \cdot 10^{-6}$
70	$2.2 \cdot 10^{-5}$
80	$7.5 \cdot 10^{-5}$
90	$2.3 \cdot 10^{-4}$
100	$6.7 \cdot 10^{-4}$
120	$4.4 \cdot 10^{-3}$
140	$2.2 \cdot 10^{-2}$
160	0.09
180	0.31
200	0.95
220	2.6
240	6.2
260	13.9
270	20.2

Antoine constants for (P in bar; T in °C) $\ln P = A + B/(C + T)$

$A = 11.6057$
$B = -6601.25$
$C = 155.61$

(The Antoine constants were determined from vapour pressure data measured in the temperature range of 190 to 270 °C by a dynamic method in a nitrogen atmosphere. The values in the table were calculated using the Antoine equation. The data serve only as a rough guide.)

Density/viscosity	Temp. [°C]	Density* ρ [g/cm^3]	Dyn. viscosity** η [mPa·s]
	5	0.9597	135
	10	0.9560	96
	20	0.9486	52
	30	0.9415	30
	40	0.9344	19
	50	0.9273	13

* *Calculated using the following equation:* ρ = **(−0.00072T + 0.96205)** *from data measured by BASF SE. (ρ = Density in g/cm^3, T = Temperature in °C)*
** *Calculated by multiplying the measured kinematic viscosity (DIN 51562) with the density.*

Solution temperature at the clear point (5 % S-PVC; K-value 71; DIN 53408) — 151 °C

Surface tension at 20 °C (DIN EN 14370) — 30.7 mN/m

Saponification value (DIN EN ISO 3681) — 264 mgKOH/g

Analytical data
Gas chromatography

The following conditions have been established in practice for the chromatographic assay:

Column:	Capillary column (polyethylene glycol) Typ CP-Wax 52CB® 1* 25 m long, internal diameter 0.25 mm Film thickness: 0.2 µm	
Temperatures:	Injector:	265 °C (with Split)
	Oven:	60 °C isotherm, then heated to 250 °C at 3 °C/min, 250 °C: 52 min
	Detektor:	300 °C
Carrier gas:	Nitrogen, high purity (approx. 1ml/min; pressure 110 KPa)** or helium	
Detector:	FID (H_2/synthetic air ratio approx. 1 : 10)** Make-up gas**	
Evaluation:	Area percent	

* = *Registered trademark of Varian, Inc.*
** = *Guide values; should be optimized for the instrument used.*

Storage

Hexamoll DINCH can be stored in suitable containers at temperatures below 40 °C and the exclusion of humidity for at least 1 year.

Literature (selection)

[1] Technical Information Leaflet of BASF SE:
"Gas chromatographic determination of the degree of purity – Solvents and plasticizers (a review)".
(TI – CIW/ES 001 d).

Safety

When using this product, the information and advice given in our **Safety Data Sheet** should be observed. Due attention should also be given to the **precautions** necessary for handling chemicals.

Note

The data contained in this publication are based on our current knowledge and experience. In view of the many factors that may affect processing and application of our product, these data do not relieve processors from carrying out their own investigations and tests; neither do these data imply any guarantee of certain properties, nor the suitability of the product for a specific purpose. Any descriptions, drawings, photographs, data, proportions, weights etc. given herein may change without prior information and do not constitute the agreed contractual quality of the product. It is the responsibility of the recipient of our products to ensure that any proprietary rights and existing laws and legislation are observed. Responsibility for compliance with textile dealers' requirements rests with the textile processor.

January 2008

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EUROPEAN COMMISSION

Health & Consumer Protection
Directorate-General

Scientific Committee on Emerging and Newly-Identified Health Risks

SCENIHR

OPINION ON

THE SAFETY OF MEDICAL DEVICES CONTAINING DEHP-PLASTICIZED PVC OR OTHER PLASTICIZERS ON NEONATES AND OTHER GROUPS POSSIBLY AT RISK

Scientific Committees

- on consumer products
- on emerging and newly identified health risks
- on health and environmental risks

Adopted after public consultation by the SCENIHR
during the 22nd Plenary of 6 February 2008

Contact:
European Commission
Health & Consumer Protection DG
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http://ec.europa.eu/health/ph_risk/risk_en.htm

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ABSTRACT

The Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) has evaluated the exposure to DEHP for the general population and patients during medical procedures. In some cases the exposure is significant and exceeds the toxic doses observed in animal studies. There is limited evidence suggesting a relation between DEHP exposures and some effects in humans. There is a reason for some concern for prematurely born male neonates for which the DEHP exposure may be transiently above the dose inducing reproductive toxicity in animal studies. Sofar, there is no conclusive scientific evidence that DEHP exposure via medical treatments has harmful effects in humans. But, it is recognised that especially the potentially high exposure during medical treatments may raise a concern, even in the absence of clinical or epidemiological evidence, for harmful effects in humans. Further studies are required to confirm or reject the suggestions of adverse effects of DEHP in humans. For certain uses of DEHP alternative plasticizers for PVC are available. The Committee got access to toxicity data for eight possible alternative plasticizers and compared their toxicity with that of DEHP. In respect to reproductive toxicity in animal studies DEHP induces more severe effects compared with some of the alternatives. A risk assessment of these available alternative plasticizers could not be performed due to a lack of exposure data from medical devices. Each alternative to DEHP, however, must also be evaluated with regard to their functionality in respect to medical devices. The risk and benefits of using alternative plasticizers should be evaluated case by case.

Keywords: SCENIHR, scientific opinion, DEHP, medical devices, neonates, alternative plasticizer, risk

Opinion to be cited as:

SCENIHR (Scientific Committee on Emerging and Newly-Identified Health Risks), Scientific opinion on the safety of medical devices containing DEHP-plasticized PVC or other plasticizers on neonates and other groups possibly at risk, 6 February 2008

EXECUTIVE SUMMARY

The Scientific Committee on Medicinal Products and Medical Devices (SCMPMD) published its Opinion on Medical Devices containing Di-(2-ethylhexyl)phthalate (DEHP) plasticized PVC in 2002. That Opinion stated that there were no reports concerning any adverse effects in humans following exposure to DEHP-PVC, even in neonates or other groups of relatively high exposure. In addition, there were no indications that neonates of high DEHP exposure have any altered long term fertility patterns. Since 2002, substantial new information on exposure to DEHP has become available as well as data on toxicity obtained in laboratory animal and human studies. Also for DEHP a so called tolerable daily intake (TDI) was calculated in recent risk evaluations. Therefore an overview is presented on the safety of DEHP in medical devices. In addition, the availability, suitability and safety of alternative plasticizers for DEHP have been evaluated. Alternative materials for PVC were not evaluated.

Certain medical procedures used in high risk groups result in a significant exposure to DEHP. In view of the reproductive toxicity observed in animal studies in which young immature animals were more susceptible to DEHP toxicity, newborn and pre-term born male infants are of special concern. Exchange transfusion in neonates, total parenteral nutrition in neonates, multiple procedures in sick neonates, and haemodialysis in peripuberal males are examples of procedures applied in high risk groups. Other risk groups are the male foetus and male infant of pregnant women or lactating women, respectively, in haemodialysis. Also massive infusion of blood into trauma patients is of concern due to exposure levels substantially exceeding the TDI of DEHP.

The toxicity of DEHP in laboratory animals is summarized. The reproductive effect of DEHP in developing and postnatal pups appears at low levels with a TDI of 48 µg/kg bw/d, derived from a three generation study in rats with a No Observed Adverse Effect Level (NOAEL) of 4.8 mg/kg bw and applying a uncertainty factor of 100.

Possible alternative plasticizers were evaluated for their potential toxicity and ranked according to toxicity and leaching, or leaching resulting in exposure. For reproductive toxicity the dose of DEHP is an order of magnitude lower compared with some of the alternative plasticizers. For some of the alternative plasticizers a complete evaluation could not be performed due to lack of data on either toxicity or exposure.

There are some studies published on the leaching of plasticizers from PVC materials to different fluids, but due to the very different conditions used it is difficult to compare the results between those studies. For most of the alternative plasticizers added in similar concentrations to PVC as the DEHP, the leaching in fatty medium appears to be the same order of magnitude. Although different leaching rates, both lower and higher, of some alternative PVC plasticizers in aqueous medium has been observed; the plasticizers leaching rate in aqueous medium are at least 1000 times lower than those in vegetable oils.

Some alternatives may be suitable to replace DEHP in certain medical devices, while for other devices it may be difficult to achieve the same functionality as PVC plasticized with DEHP. The risk and benefit of using alternative plasticizers should be evaluated case by case.

Compared to the previous opinion of the SCMPMD, the new information on DEHP indicates that there is still a reason for some concern for prematurely born male neonates. This concern is instigated by the potential high human exposure to DEHP especially during certain medical procedures which may be transiently above the dose inducing reproductive toxicity in animal studies.

Sofar, there is no conclusive scientific evidence that DEHP exposure via medical treatments has harmful effects in humans. However, it is recognised that especially the potentially high exposure during medical treatments may raise a concern, even in the absence of clinical or epidemiological evidence, for harmful effects in humans. Further studies are required to confirm or reject the suggestions of adverse effects of DEHP in humans.

TABLE OF CONTENTS

1. BACKGROUND

According to Council Directive 93/42/EEC, Medical Devices may only be placed on the market if they meet the essential requirements laid down in the Annex I of the Directive.

For certain medical procedures such as blood transfusion, haemodialysis, parenteral nutrition or endotracheal tubing, the flexibility of certain parts of a medical device is essential. Various substances are used to ensure this flexibility, among which DEHP [Di-(2-EthylHexyl) Phthalate] is the most frequently used plasticizer in PVC medical devices. DEHP may migrate from the device to the human body, resulting in a certain degree of patient exposure.

Safety concerns have been expressed for high-risk patients groups, such as neonates, infants, pregnant and breast-feeding women exposed to DEHP. In September 2002, the Scientific Committee on Medicinal Products and Medical Devices adopted an opinion on "Medical Devices containing DEHP plasticized PVC; Neonates and Other Groups Possibly at Risk from DEHP toxicity" according to which "there is no evidence that any of these groups do experience DEHP related adverse effects". However, "a lack of evidence of causation between DEHP-PVC and any disease or adverse effect does not mean that there are no risks".

According to published data on reproduction toxicity, neonates and prepubertal males may suffer adverse effects from DEHP exposure in medical devices. According to a recent risk evaluation of DEHP on human health carried out in the context of the "existing" chemicals substances legal framework, a Tolerable Daily Intake (TDI) of DEHP was determined for the general exposure of humans to DEHP.

It is therefore necessary for the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) to review and possibly update the opinion adopted in 2002. Since alternative DEHP-free medical devices have been recently introduced in the market, the long-term effect of these alternative plasticizers or alternative materials, when used in medical devices, are not well known. In view of possible safety concerns linked to the use of DEHP in PVC plasticized medical devices, it is essential to review and evaluate available scientific data related to the safety of these alternatives for patients and in particular to high risk groups.

2. TERMS OF REFERENCE

1. Update of the scientific opinion adopted in September 2002 on DEHP plasticized medical devices. Taking into consideration recent scientific developments, the SCENIHR is requested to review and update, if appropriate, the scientific opinion adopted in September 2002 on "Medical Devices containing DEHP Plasticized PVC; neonates and other groups possibly at risk from DEHP toxicity".

In particular, the Scientific Committee is requested to evaluate:

- *If DEHP in PVC plasticized medical devices is a cause for concern to neonates and children in paediatric care, in particular in relation to male fertility and tissue development,*
- *If there are other patient groups at risk, in particular in view of clinical procedures resulting in high exposure,*
- *If it is possible to establish Tolerable Intake Values of DEHP leaching from soft PVC as a basis for risk assessment for high risk patient groups, taking into account the route of exposure.*

2. Medical devices containing alternative plasticizers: possible risk for certain uses or to certain patient groups. Since alternative DEHP free medical devices have been developed and are used to treat patients, the Scientific Committee is requested to evaluate the potential risks of currently available alternatives in relation to patient health, when used in medical devices.

3. SCIENTIFIC RATIONALE

3.1. Introduction

In view of the complexity of the questions addressed in the Terms of Reference. the Committee decided to concentrate on the risk assessment of plasticizers used in PVC in this opinion. Whilst recognising that there are several non-PVC based materials that could provide effective materials for use in medical devices, this opinion does not address these materials. Although the published Call for Information included both alternative plasticizers and alternative materials, only the former was submitted. The Committee recognized that there may be need for evaluation of these alternative non-PVC materials in the future.

Polyvinylchloride (PVC) is used extensively for a very wide range of purposes ranging from a lining for landfill waste disposal sites to a food wrapper for foods. One of the key attributes of PVC that has led to its widespread use is its stability and flexibility, which is achieved by the incorporation of plasticizers in particular phthalates.

The use of PVC in medical devices represents a very minor percentage of the total amounts of PVC manufactured each year. Nonetheless the use of plasticized PVC in a wide range of medical devices has been very important for a number of reasons:

- flexibility in a variety of physical forms from tubes to membranes
- chemical stability and possibility to sterilise.
- low cost and wide availability.
- lack of evidence of significant adverse consequences in patients.

A plasticizer is a substance which when added to a material, usually a polymer, makes it flexible, resilient and easier to handle. There are more than 300 different types of plasticizers described of which between 50 and 100 are in commercial use. The most commonly used plasticizers are phthalates. In Western Europe about one million tonnes of phthalates are produced each year, of which approximately 900,000 tonnes are used to plasticize PVC (http://www.plasticisers.org). The most common are: di-iso-nonyl phthalate (DINP) di-iso-decyl phthalate (DIDP) and di(2-ethylhexyl) phthalate (DEHP). Plasticizers are used in a variety of PVC based products such as electrical cables, toys, footwear, packaging, building materials, paints, rubber products, adhesives and cosmetics. PVC containing plasticizers are also used for the production of medical devices such as medical tubing and blood bags. There is a reduction in the use of DEHP as plasticizer in PVC (personal communication, ECPI 2007).

Secondary plasticizers, also known as extenders, also play a role in flexible PVC formulations. Chlorinated paraffins (CPs), epoxidised soya bean oil (ESBO) and epoxidised linseed oil (ELO) are commonly used secondary plasticizers. CPs also act as flame retardants, ELO and ESBO as lubricants and also as secondary stabilisers to PVC due to their epoxy content, which can remove hydrochloric acid from the degrading polymer. Plasticizers are not chemically bound to PVC, and may therefore leach (leak, migrate) into the surrounding environment. In this opinion the term leach will be used for consistency.

The biological properties of the phthalate plasticizers used in PVC, especially DEHP, have been the subject of a very substantial amount of research. As a consequence concerns have been raised about the implications for human health and to the environment of three particular properties of DEHP observed in experimental animals/other experimental systems namely the potential to cause:

- reproductive and developmental effects.
- endocrine disruption and testes toxicity.
- peroxisome proliferation in the liver and thereby increase the incidence of liver cancer in rodents.

Reports on these properties have resulted in calls from various organisations and individuals to replace DEHP with other plasticizers that do not show such properties.

In addition a number of bodies have called for a reduction in PVC use or even an outright ban on PVC itself because of their concerns about the environmental problems associated with PVC disposal, especially the production of dioxins as a result of the incineration of PVC. However, recently there have been improvements in the incineration technologies in Europe such that the PVC incineration minimises dioxin emission (Danish EPA 2003).

The above concerns have resulted in the SCENIHR being asked by the Commission Services to review and where appropriate update the Opinion of its predecessor committee (The Scientific Committee on Medical Products and Medical Devices Opinion (SCMPMD) of September 2002) on the risks and benefits of the use of PVC, incorporating DEHP, in medical devices. Possible alternative materials could not be evaluated in view of the lack of an analysis of the risks associated with these materials at that moment. However, it was concluded that some alternative plasticizers could replace DEHP in PVC on some conditions for which evaluation of risk and benefits should be done on a case by case basis.

In 2002 Health Canada (2002) recommended that alternative products that are already available should be utilized for all ECMO (extracorporeal membrane oxygenation) procedures in newborns and infants. Tubing and storage bags used for administration of lipophilic drugs or drugs which contain surfactants (i.e., lipophilic drug formulations) should not contain DEHP, or strategies to decrease DEHP exposure should be employed, particularly when administering these drugs to infants and children. As alternative products are already available, it was recommended that total parenteral nutrition solutions be administered to newborn and infants only via products, which do not contain DEHP. At that time the Food and Drug Administration (FDA) of USA was recommending the manufactures of medical devices to consider eliminating the use of DEHP in such devices that can result in high exposure in sensitive patients and that certain products be labelled with their DEHP content (FDA 2002).

The SCENIHR decided that in order to address this request a risk assessment needed to be carried out in which PVC containing DEHP should be the benchmark. It was also agreed that the evaluation should concentrate on new information that was not available to the SCMPMD in its deliberations in 2002.

DEHP is the main plasticizer used in PVC based medical devices. According to European Pharmacopoeia, only DEHP, ESBO and ELO should be used as plasticizers in medical devices (Medical Devices Directive 93/42/EEC). A number of other substances are used as plasticizers in medical devices (for example, butyl trihexyl citrate in blood bags), and some non-PVC based materials (for example, enteral feeding bags made of ethyl vinyl acetate) are also available as alternative to DEHP-PVC. In order to obtain the most updated information the Commission published a Call for Information in March 2006 inviting interested parties to submit:

1) Scientific peer reviewed research papers and reviews (later than 1995) on this issue.
2) Data on safety evaluation.
3) Other publicly available credible scientific information that may not be easily available and which is directly relevant to this issue.

The results of this Call for Information and information available from other sources were used as a basis for the following evaluation on DEHP and its alternatives in PVC medical devices. Consequently in this report only the risks from DEHP and possible alternative plasticizers for which sufficient suitable information has been provided are considered. Information on the following compounds was obtained from the stakeholders:

- Glycerides, Castor-oil-mono-, hydrogenated, acetates (COMGHA, CAS 736150-63-3)
- Acetyl-tri-n-butyl citrate (ATBC, CAS 77-90-7)
- n-Butyryl-tri-n-hexyl citrate (BTHC, CAS 82469-79-2)
- Di-iso-nonyl-1,2-cyclohexanedicarboxylate (DINCH, CAS 166412-78-8)
- Dioctyl terephthalate (DOTP, CAS 6422-86-2)
- Trioctyl trimellitate (TOTM, CAS 3319-31-1)

In addition, other phthalates could be used in medical devices and SCENIHR also looked for information for these substances. A compound that is used as plasticizer in food packaging materials, DEHA, was also added to the list which thus also contains the following substances:

- Di-iso-nonyl phthalate (DINP, CAS 68515-48-0 and 28553-12-0)
- Di(2-ethylhexyl) adipate (DEHA, CAS 103-23-1)

Also polymeric plasticizers such as aliphatic polyesters can potentially be used as alternative plasticizers in PVC medical devices.

It must also be emphasised that in the following evaluation only risks and health benefits to patients who are exposed to medical devices are considered. Thus the following risk/benefit considerations are excluded from our consideration:

- Health, safety and environmental aspects of PVC manufacture and incorporation into medical devices.
- Health and safety of medical and ancillary staff handling or otherwise exposed to PVC medical devices and any substances released from them.
- Environmental risks associated with disposal of PVC containing medical devices.

The focus of this opinion is on the possible risk for patients exposed to medical devices, but as there is a considerable exposure to plasticizers for the general public, this has been taken into account in the evaluation.

The safety assessment performed here includes currently available as well as proposed alternatives of DEHP in medical devices for neonates and for other patient groups, in particular in view of clinical procedures resulting in high exposure. Thus, important medical devices (blood bags, catheters, dialysis equipment, enteral feed containers, gastrointestinal tubes, IV solution storage and administration sets, tubing used in neonates, tubing used for respiratory therapy and containers for total parenteral nutrition (TPN)) and potential DEHP alternatives are the focus of the evaluation.

Finally it is pertinent to point out that only the risks from the use of plasticizers in PVC medical devices have been evaluated. The SCENIHR was not requested to consider the health risks from other substances that might leach out of a PVC medical device such as stabilisers, other additives and contaminants.

In the following chapters the data on DEHP are considered first which is followed by a comparison with the biological properties of the other plasticizers.

3.2. Present use of plasticized PVC in medical devices

Quantitative information of the amount of plasticized PVC used for medical devices is not available. Medical applications account for 0.5% of the total PVC volume used in Western Europe[1]. The world PVC use was 2.94×10^7 t in 2004 with a 4.3% annual growth rate[3]. The Western European use is approximately 5.8×10^6 t. According to the EU life cycle assessment

[1] Final Report of EU-Contract No. ETD/FIF.20020892: Life Cycle Assessment of PVC and of principal competing materials

report medical applications account for 0.5% of the PVC used in Europe. Thus approximately 3×10^4 t of plasticized PVC is used for medical applications annually in Europe.

It is possible to greatly reduce the use of DEHP-PVC in hospital procedures as demonstrated in several hospitals around Europe. This might be achieved by using PVC containing alternative plasticizers or using alternative materials. However, this probably can not be achieved for all medical procedures.

DEHP is used in PVC to manufacture blood bags. DEHP is leaching into the blood in which it contributes to the stability and survival by stabilising the red blood cell membrane (Labow et al. 1987). This prolongs the possibilities of blood storage up to 6-8 weeks after blood collection. Similar effects have also been demonstrated with some other alternative plasticizers in PVC blood bags. This effect may need to be taken into account in the risk-benefit evaluations of the PVC plasticizers.

The use of plastics in medical application is increasing and the medical plastics market was anticipated to grow by more than 3% annually in 2005. There is also a considerable interest from medical plastic producers in developing alternative materials to plasticized PVC.

3.3. Physicochemical properties of plasticizers

The most important physical parameters for evaluating potential human and environmental exposures are water solubility, octanol/water partition coefficient and leaching data. Furthermore the vapour pressure of the plasticizers at the use temperature may in some cases be important. Whereas the solubility and vapour pressure data are available to some extent, very little information is available on leaching.

Table 1 summarizes important physical chemical characteristic, some of which have been estimated (in Italics in the table) limiting their validity. It is possible to predict the relative exposure to be expected from the use of different plasticizers. The rate of leaching is dependent on the lipophilicity of the compound and of the material stored, duration of storage, storage temperature, contact area and, in some cases, agitation. In general, the plasticizers show a higher extent of leaching in lipophilic solutions. The clearest conclusion that can be drawn is that there is a severe lack of data on solubility, water/oil partition coefficients and especially leaching of the plasticizers under conditions relevant to the usage in plasticized products.

Table 1. Overview of some physical properties of the assessed plasticizers.

Substance	Vapor pressure at 20°C (Pa)	Water Solubility (µg/L)	log K_{ow}	Water extractability (%)[a]	Kerosene extractability (%)[b]
COMGHA	<2.8 x 10^{-4} at 100ºC (4)	7 x 10^{3} (4)	6.0 - 7.7 (4)		
ATBC	6 x 10^{-4} (3)	6 x 10^{2} (3)	4.3 (3)		
BTHC	8 x 10^{-8} (3)	6 x 10^{-2} (3)	8.2 (3)		
DEHA	4 x 10^{-4} (3)	0.5 (3)	8.1 (3)	0.10	>70
DEHP	3.4 x 10^{-5} (1)	3.0 (1)	7,5 (1)	0.01	44.3
DINCH	<2.8 x 10^{-4} at 100ºC (4)	<20 (4)	10.0 (4)		
DINP	6 x 10^{-5} (2)	0.6 (2)	8.8 (2)	0.07	77
DOTP	3 x 10^{-3} (3)	1 (3)	8.3 (3)	0.09	71
TOTM	8 x 10^{-6} (3)	6 x 10^{-3} (3)	11 (3)	0.0	>70

a: Loss of plasticizers from a 1 mm, PVC sheet containing 40 wt % plasticizer when extracted with water at 50°C for 24 hours (ASTM D1239-55 (from Sears, 1989).

b: Loss of plasticizers from a 1 mm, PVC sheet containing 40 wt % plasticizer when extracted with kerosene at 23°C for 24 hours (ASTM D1239-55 (from Sears, 1989). The kerosene extractability is an indicator of lipid solubility.

1: ECB 2001: (http://ecb.jrc.it/DOCUMENTS/Existing-Chemicals/RISK_ASSESSMENT/DRAFT/R042_0310_env_hh_combined.pdf)

2: ECB 2003: (http://ecb.jrc.it/DOCUMENTS/Existing-Chemicals/RISK_ASSESSMENT/REPORT/dinpreport046.pdf)

3: Estimated with EPISUITE 3.20 (http://www.epa.gov/opptintr/exposure/pubs/episuite.htm)

4: From dossier (see Annex)

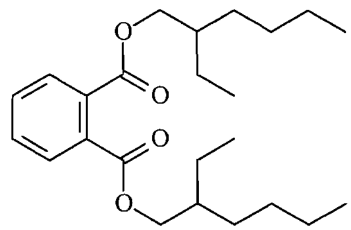
As can be seen in Table 1 the assessed plasticizers are very lipophilic, and all of them, except ATBC, have log K_{ow} values above 7 and low water solubility. In this respect the alternatives are not very different from DEHP. The leaching of these substances from PVC to body fluids/tissues can thus be expected to be of similar magnitude compared with DEHP with the possible exception of ATBC.

3.4. DEHP (di(2-ethylhexyl) phthalate)

3.4.1. Physico-chemical properties

The evaluation of DEHP is included in this Opinion as a basis for comparison with the different alternatives. The chemical characteristics of DEHP are presented below.

CAS Reg. No.: 117-81-7
Synonyms:
Emperical formula: $C_{24} H_{38}O_4$
Structure:



Molecular weight:	390.6
Melting point:	-50°C
Boiling point:	385°C
Vapour pressure:	0.000034 Pa (20°C)
Solubility in water:	0.003 mg/L
Log K_{ow}:	7.5
Purity:	99.7%
Impurities:	Other phthalates. Up to 0.5% Bisphenol A is added to some products[2].

3.4.2. Use

The use of DEHP in Europe 1997 has been estimated to 476,000 ton and about 97% of that is used as plasticizer in polymers, mainly PVC (personal communication, ECPI 2007). About 22% of that is used for products with mainly outdoor applications, while the remaining 462,000 tons end up in products being used indoors. The use in medical devices is estimated at 0.5% of the total production of which the major use (more than 95%) is soft medical grade PVC in containers, flexible tubing and medical gloves. The typical concentration of DEHP in plasticized PVC is 30% (ECB 2004).

3.4.3. Metabolism of DEHP in humans

In mammals, including man, DEHP is converted into a variety of metabolites (Figure 1). The first and fast stage in the metabolism of DEHP is the hydrolytic cleavage to mono(2-ethylhexyl) phthalate (MEHP) and 2-ethylhexanol (2-EH). After oral uptake enzymatic hydrolysis occurs already in mouth (Niino et al. 2003, Niino et al. 2001) and especially in the gastrointestinal tract (Albro et al. 1982, Albro and Thomas 1973). Thus it can be assumed that the majority of DEHP is rapidly absorbed as MEHP in gut following oral administration. DEHP hydrolyzing lipases can be found in many tissues (especially in pancreas, intestinal mucosa, liver) and in blood plasma of rats (Albro and Thomas 1973, Daniel and Bratt 1974).

[2] ECPI informed that DEHP formulations used for medical devices do not contain bisphenol A

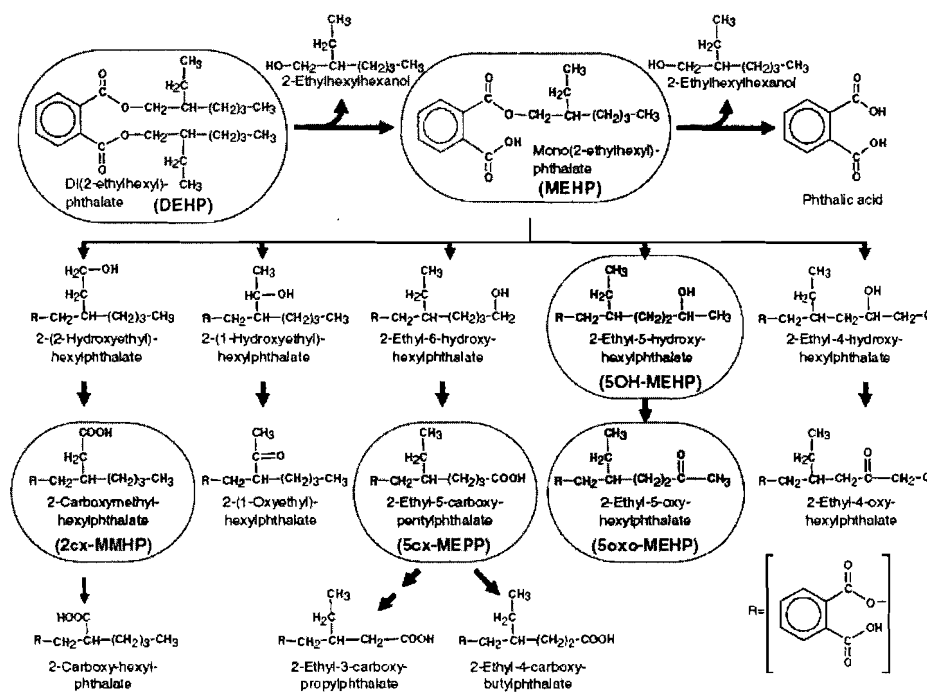


Figure 1. DEHP metabolism[3] (according to Albro 1982, Peck and Albro 1982, Schmid and Schlatter 1985). Major metabolites according to Koch (2005a) are highlighted.

Further metabolism takes place in the liver (Albro 1986) with 2-EH and MEHP undergoing a set of oxidative reactions. In rats the formed 2-EH is rapidly metabolized to 2-ethylhexanoic acid, which is further oxidised by ω- and (ω-1)-oxidation and subsequent β-oxidation to acetate and CO_2 (Albro 1975). Also in human urine several of these oxidative metabolites have been identified (Wahl et al. 2004, Wahl et al. 2001).

MEHP is metabolized to produce a large number of oxidative metabolites (Figure 1). Oxidative metabolism of MEHP starts with hydroxylation of the alkyl chain at various positions and the formation of primary (ω-oxidation) and secondary alcohols (ω-n-oxidation). These hydroxylated products can undergo further oxidative reactions to the respective ketones and carboxylic acids. After that the carboxylated alkyl chain can be subject to α- or β-oxidation to yield shorter carboxylated alkyl chains (Albro et al. 1982, Albro et al. 1983, Peck and Abro 1982, Schmid and Slatter 1985).

In previous human metabolism studies urinary excretion rates between 10 and 31% after oral DEHP administration were determined determined , which indicated a maximal oral bioavailability of 50% as well (ECB 2004). However, Koch et al. (2004b, 2005a) found that the majority of orally administered DEHP is systemically absorbed in humans and excreted via urine. After two days of administration of deuterium ring-labelled DEHP (0.35 mg, 2.15 mg and 48.5 mg) to a male healthy volunteer about 75% of the dose was excreted in urine in form of the five major metabolites mono(2-ethyl-5-hydroxyhexyl) phthalate (5OH-MEHP) (24.7%), mono-(2-ethyl-5-carboxypentyl) phthalate (5cx-MEPP) (21.9%), mono(2-ethyl-5-

[3] Figure provided by Koch et al. 2005. New metabolites of di(2-ethylhexyl)phthalate (DEHP) in human urine and serum after single oral doses of deuterium-labelled DEHP. Archives Toxicology 2005; 79: 367-76 (Figure 1). With kind permission of Springer Science and Business Media and the approval of the author.

oxohexyl) phthalate (5oxo-MEHP) (14.9%), MEHP (7.3%) and mono[2-(carboxymethyl)hexyl] phthalate (2cx-MMHP) (5.4%). No dose dependency in metabolism and excretion was observed for the dose range investigated. Taking into account that further minor DEHP metabolites, such as mono(2-ethyl-3-carboxypropyl) phthalate, mono(2-ethyl-4-carboxybutyl) phthalate, and mono(2-(1-oxoethyl)hexyl) phthalate, were excreted in human urine (Figure 1) (Albro et al. 1982, Schmid and Slatter 1985, Silva et al. 2006a) and so far only periods up to 48 h after administration were observed one can assume that the majority of an orally taken DEHP dose is absorbed and excreted via urine.

In rats and non-human primates absorption rates of around 50% for doses up to about 200 mg/kg have been estimated (ECB 2004). In contrast to rodents there may be a dose-limited absorption at higher doses (2000 mg/kg per day for 14 days) in non-human primates (Rhodes et al. 1983, Rhodes et al. 1986).

Koch et al. (2004b, 2005a) found that urinary excretion in human followed at least a two-phase elimination model. The first elimination phase (after 4-8 h absorption and distribution) lasted until 14-16 h after D4-DEHP administration, with an elimination half-life of about 2 h for all five metabolites. In the second elimination phase considerably longer half-lives were estimated for the oxidized DEHP metabolites 2cx-MMHP (24 h), 5cx-MEPP (12-15 h), 5OH-MEHP (10 h), 5oxo-MEHP (10 h) than for the simple monoester MEHP (5 h). The respective half-lives in serum were estimated to be shorter than two hours except for 2cx-MMHP, for which the half-life was at least 5h. In contrast to urine MEHP was seen to be the dominant metabolite in serum.

After normalization Koch et al. (2005a) calculated a 15–100 times higher normalized area under the concentration-time curve for MEHP in human blood than previously found in rats and marmosets (Kessler et al., 2004). In the latter study the normalized AUCs of marmosets were found to be up to 16 times lower than in rats receiving the same daily oral DEHP dose per kilogram of body weight. This may indicate that a similar external exposure to DEHP results in a higher internal dose to MEHP in humans compared to rats and particularly to marmosets.

After long-term exposure, which generally may occur in the general population, the ratios among the DEHP metabolites excreted in urine seem to be shifted in favour to the metabolites with longer half-lives. In population studies 5cx-MEPP was found to be the principal urinary metabolite, followed by 5OH-MEHP, 5oxo-MEHP, 2cx-MEHP, and MEHP (Preuss et al. 2005, Silva et al. 2006b).

Apart from the first hydrolysis step to MEHP the metabolism of DEHP appears to be qualitatively unaffected by the route of administration (ECB 2004). After intravenous exposure to DEHP via a voluntary platelet donation the secondary metabolites 5OH-MEHP, 5cx-MEPP and 5oxo-MEHP were the major urinary metabolites followed in some distance by the simple monoester MEHP and 2cx-MMHP (Koch et al. 2005a, Koch et al. 2005b). Furthermore, the elimination characteristics and relative distribution of the DEHP metabolites in urine were found to be rather similar to that after oral administration (Table 2), which indicates that the toxicokinetic behaviour of DEHP in humans is not different for those exposure routes.

Several studies indicate some differences in DEHP metabolism between species. In rats 5cx-MEPP was found to be the predominant DEHP metabolite in urine, whereas in mice it seems to be only a minor metabolic product (Peck and Albro 1982). On the other hand rats excrete much lower amounts of MEHP compared to other mammalians including primates (Peck and Albro 1982). β-oxidation may be a major metabolic pathway in rodents but not in primates and humans (Albro et al. 1982). After intravenous administration of DEHP quite similar profile of the urinary metabolites were determined in Green monkeys and humans by Albro et al. (1981) and Peck et al. (1978). In these studies, however, 5OH-MEHP and MEHP were identified as the major metabolites, whereas the relative amounts of 5cx-MEPP were clearly lower, which is in some contrast to the recent findings from Koch et al. (2004b, 2005a).

Glucuronidation is the major conjugation pathway in mice, guinea pigs and non-human primates (Albro et al. 1982, Egestad et al. 1996). Earlier studies suggest that glucuronides are not formed in rat (Albro et al. 1982, Kluwe 1982). In a recent human study MEHP was mostly found as glucuronide conjugate in maternal urine (Calafat et al. 2006). In humans at least 65% of the MEHP derivatives in the urine seem to be excreted as glucuronides following oral or intravenous administration (Albro et al. 1982, Bronsch 1987, Schmid and Slatter 1985). Large interindividual variations in the glucuronidation were observed for some DEHP metabolites (Dirven et al. 1993, Silva et al. 2006b). While the carboxylic acid metabolites were found to be excreted only partially in their glucuronidated form, the alcohol and ketone metabolites are excreted mainly as glucuronic acid conjugates (Silva et al. 2006b).

Table 2. Relative distribution (in %) of the five major DEHP metabolites (sum is set as 100%) in human urine after oral administration (D4-DEHP) and intravenous exposure

Route	5OH-MEHP	5cx-MEPP	5oxo-MEHP	MEHP	2cx-MMHP	Reference
Oral	34.8	27.6	22.4	8.8	6.3	Koch 2005a
Intravenous	26.4	27.2	23.1	13.3	10.0	Koch 2005b

Distribution studies in rodents indicate that DEHP is widely distributed in the tissues without evidence of accumulation (Daniel and Bratt 1974, Gaunt and Butterworth 1982, Pollack et al. 1985a). After oral administration of ^{14}C-DEHP rats and marmosets showed qualitatively similar distribution patterns (liver>kidney>testes) (Rhodes et al. 1986). DEHP and its metabolites may be secreted into the milk of lactating rats (Dostal et al. 1987, Parmar et al. 1985) and also pass into human milk (Bruns-Weller and Pfjordt 2000, Calafat et al. 2004b, Gruber et al. 1998, Mortensen et al. 2005, Zhu et al. 2006). In rodents ^{14}C-DEHP was found to cross the placenta and distribute into foetal tissues (Lindgren et al. 1982, Singh et al. 1975, Srivastava et al. 1989). The monoester MEHP was found in rat and human amniotic fluid (Calafat et al. 2006, Silva et al. 2004b).

The data regarding metabolism and bioavailability following inhalation and dermal exposure are limited. With respect to inhalation no reliable human or adequate animal data in a relevant animal model are available. It can be assumed that only a fraction of the amount inhaled will be available to the lungs while the majority will probably be swallowed and become orally bioavailable (ECB 2004). The dermal absorption appears to be poor in human. Wester et al. (1998) estimated that dermal absorption amounts to approximately 1.8% of a 24-hour applied dose of ^{14}C-DEHP solubilized in ethanol. In rats the bioavailability of DEHP after dermal exposure has been estimated to be around 10% (Elsisi et al. 1989, Melnick et al. 1987). However, the results of in vitro studies (Barber et al. 1992, Scott et al. 1987) indicate that the rat skin is about 4-fold more permeable for DEHP than human skin. So, approximately 2.5% of a dermal dose may be adsorbed by human skin.

There are indications that the oxidative pathway in DEHP metabolism is a function of age. In several studies higher ratios of the oxidative metabolites 5OH-MEHP, 5oxo-MEHP and 5cx-MEPP to the simple monoester MEHP were found in children in comparison to adults (CDC 2005, Koch et al. 2004a, Silva et al. 2006b). Also among children increasing ratios with decreasing age were observed (Becker et al. 2004). In neonates there is a higher capacity for oxidation of MEHP with 5cx-MEPP being by far the principal metabolite (Egestad et al. 1996, Koch et al. 2006).

3.4.4. DEHP exposure of the general population

DEHP is only physically dispersed in PVC and can therefore leach, migrate or gas out from PVC articles. Therefore DEHP can be present in air, dust, water, soils, sediments, and food and has become a ubiquitous environmental contaminant (Clark et al. 2003b). Diet has been determined as the main source of DEHP exposure for the general population with fatty foods (e.g. dairy, fish, oils) containing the highest DEHP levels (Clark et al. 2003b, ECB 2004, Meek and Chan 1994, Peterson and Breindahl 2000, Wormuth et al. 2006). DEHP contamination of food may occur due to bioaccumulation in certain foods as well as during processing, handling, transportation, packaging and storage. Further sources of DEHP exposure are indoor air, household dust, consumer products, and medical procedures.

3.4.5. DEHP exposure assessment from probabilistic calculations

Exposure estimates based on probabilistic calculations from DEHP levels in environmental media and food are given in Table 3. The deduction of DEHP exposure from concentrations in environmental media is difficult due to the numerous sources and routes that have to be considered, and due to the uncertainties in assumptions made for the exposure assessment. Moreover, since DEHP is omnipresent in the environment contamination can easily occur during analytical procedures (David et al. 2003b). Finally, one has to consider that the calculated DEHP exposure via food might be based on outdated DEHP contents in food or that the DEHP burdens have not been corrected for background contamination (Clark et al. 2003a), which would lead to an overestimation of the DEHP exposure. The range of DEHP exposure in the general population from all sources excluding medical and occupational exposure has been estimated to be 1 to 30 µg/kg bw/d (CERHR 2005, Doull et al. 1999, Huber et al. 1996). Children are assumed to have higher exposures to DEHP than adults (Clark et al. 2003a, Meek and Chan 1994, Müller et al. 2003).

Table 3. DEHP exposure for the general population (µg/kg bw/d) estimated from DEHP contents in environmental media and food (modelling studies)

Study	Age group	Median	Upper bound (P 95, max)
Meek (1994) [a]	20-70 years	5.8	
	12-19 years	8.2	
	5-11 years	14	
	0.5-4 years	19	
	0-0.5 years	9	
MAFF (1996) [b]	Adults	2.5	5
Clark (2003a) [c]	Adult (20-70 years)	8.2	
	Teen (12-19 years)	10	
	Child (5-11 years)	18.9	
	Toddler (7 months-4 years)	25.8	
	Infant (0-6 months)	5-7.3	
Müller (2003) [d]	Adults		26
	children (7-14 years)		49
	children (1-6)		151
	infant 6-12 months		285
Wormuth (2006) [e]	Children	1.8	15.8
	Adults	2.7	15.5

a estimated daily DEHP exposure from air, food, drinking water by the population of Canada
b dietary exposure in UK
c considering all exposure pathways excluding children's and other consumer products
d combined oral, inhalatory and dermal exposure via several pathways in Denmark
e scenario-based approach including oral, dermal and inhalation pathways for Europeans

3.4.6. DEHP exposure assessment from urinary metabolite excretion

The individual and actual internal exposure to DEHP can be determined by measuring DEHP metabolites in urine (Blount et al. 2000, Koch et al. 2006, Koch et al. 2003b). Specific urinary DEHP metabolites can serve as biomarkers of DEHP exposure covering all sources and routes of exposure. So far, urinary levels of DEHP metabolites have been measured in several studies in Germany and USA, which have revealed the ubiquitous exposure of the general population to DEHP (Table 4). The data from both countries are in good accordance and lie within the same order of magnitude. While in the first studies only the simple monoester MEHP has been determined in urine, the parameter spectrum has been steadily increasing. By now the secondary metabolites have been recognized as much more reliable biomarkers for an assessment of the DEHP exposure (Koch et al. 2006, Koch et al. 2003b). They are excreted to a higher extent than MEHP and are more specific as they are not susceptible to contamination. By contrast, MEHP can be formed by hydrolysis of DEHP during sample handling and processing. Mono(2-ethyl-5-carboxypentyl) phthalate (5cx-MEPP) was found to be the main urinary metabolite measured in the general population, followed by mono(2-ethyl-5-hydroxyhexyl) phthalate (5OH-MEHP), mono(2-ethyl-5-oxohexyl) phthalate (5oxo-MEHP), mono(2-ethylhexyl) phthalate (MEHP), and mono(2-carboxy-methylhexyl) phthalate (2cx-MMHP) (Table 4). This is partly in contrast to the metabolic excretion pattern found after a single dose of D4-DEHP (Koch et al. 2005a) with 5OH-MEHP as the main metabolite. However, due to the chronic exposure in the general population the ratios may be shifted to the metabolites with the longest half-lives, which are the carboxy metabolites. In general, children showed higher concentrations of DEHP metabolites than adults with higher ratios of the oxidative metabolites compared to MEHP (Becker et al. 2004, CDC 2005, Koch et al. 2004a).

Table 4. Median body burden to DEHP of the general population, indicated by urinary concentrations of DEHP metabolites (in µg/l)

Study	Year of sampling	n (age)	5cx-MEPP	5OH-MEHP	5oxo-MEHP	2cx-MMHP	MEHP	FOD*	DEHP^{+} [µg/kg/day]
Blount (2000)[1]	1988-1994	298 (20-60)	n.d.	n.d.	n.d.	n.d.	2.7	>75	1.3
Koch (2003b)[2]	2002	85 (7-63)	n.d.	46.8	36.5	n.d.	10.3	100	5.8
Barr (2003)[1]	n.s.	62 (n.s.)	n.d.	35.9	28.3	n.d.	4.5	96	4.3
Silva (2004a)[1]	1999/2000	2541 (>6)	n.d.	n.d.	n.d.	n.d.	3.2	78	1.6
Becker (2004)[2]	2001/2002	254 (3-14)	n.d.	52.1	41.4	n.d.	7.2	100	(6.3)
Koch (2004a)[2]	2003	19 (2-6) 36 (adults)	n.d.	49.6 32.1	33.8 19.6	n.d.	6.6 9.0	100 100	(5.6) 3.8
Kato (2004)[1]	2001	127 (n.s.)	n.d.	17.4	15.6	n.d.	<LOD	95	2.4
CDC (2005)[1]	2001/2002	393 (6-11) 742 (12-19) 1647 (>20)	n.d.	32.9 25.2 17.7	22.6 18.5 12.2	n.d.	4.4 4.5 4.1	NA	(3.7) 3.0 2.1
Swan (2005)[1]	1999-2002	85 (>18) pregnant women	n.d.	11.4	11.1	n.d.	3.3	98	1.4
Silva (2006)[1]	2003/2004	129 (adults)	15.6	15.3	7.1	5.9	3.1	100	1.9
Wittassek (2007a)[2]	2001/2003	120 (20-29)	19.5	14.6	13.4	5.8	5.0	100	2.3

1 US population
2 German population
* Frequency of detection for at least one DEHP metabolite in %

+ Median daily intake estimation applying equation (1) assuming that creatinine related concentrations are equal to volume related concentrations and a mean creatinine excretion of 21 mg/kg/day (men and women); values for children in parentheses

n.d.: not determined

NA: not available

From the urinary concentrations measured daily DEHP exposure has been calculated by comparison with urinary excretion rates determined in human metabolism studies (Anderson et al. 2001, Koch et al. 2004b, Koch 2005a, Schmid and Slatter 1985). Since in the most metabolite excretion studies 24h urine samples were not available the amount of the DEHP metabolites excreted throughout a day has to be extrapolated from spot urine concentrations. This can be done by using reference values for the daily creatinine excretion (separately for men, women and children). For calculation of daily DEHP intake following equation has been applied:

$$\mathrm{DI}\,(\mu\mathrm{g/kg}_{\text{body weight}}/\mathrm{day}) = \frac{\mathrm{UE}_{\mathrm{met}} \cdot \mathrm{CE}}{\mathrm{F}_{\mathrm{UE}}} \cdot MW_{DEHP}$$

UE_{met} urinary excretion of one or several DEHP metabolites in µmol/g crea

CE reference value for daily creatinine excretion [g crea/kg/day]

F_{UE} molar ratio between the urinary excreted amount of DEHP metabolite(s) and the DEHP amount taken up determined in human metabolism studies

MW_{DEHP} molecular weight of DEHP

CE: women: 18 mg/kg/day
men: 23 mg/kg/day

Calculation:
Volume related concentrations ~ Creatinine related concentrations

Alternatively, also a volume based calculation model has been applied (Wittassek et al. 2007b). Ideally, 24 urine samples are collected for a daily DEHP intake estimation as the absolute amount of the excreted DEHP metabolites during a whole day is directly accessible (Wittassek et al. 2007a). However, this is laborious and e.g. for children not a realistic approach.

First daily DEHP intake evaluations were based on the excretion of the simple monoester MEHP only (David et al. 2000, Kohn et al. 2000). At that time, available metabolism studies indicated that urinary MEHP represented between 2.4% and 13% of the DEHP dose (Anderson et al. 2001, Schmid and Slatter 1985), which led to substantial differences in the resulting daily intake values depending on the excretion factor used. More recent daily intake calculations implement also the secondary DEHP metabolites (Koch et al. 2003a, Wittassek et al. 2007a, Wittassek et al. 2007b). Estimations based on three or five DEHP metabolites may lead to more reliable estimations of the daily DEHP intake.

In general, daily DEHP intake estimations based on urinary biomarkers give values in the same order of magnitude as those based on probabilistic calculations (Table 5). The current median DEHP exposure for the German general population has been estimated to be between 2 and 5 µg/kg bw/d (Koch et al. 2003a, Wittassek et al. 2007a). Children seemed to be higher exposed in relation to kg bw/ with a median exposure of around 4 to 8 µg/kg/d (Wittassek et al. 2007b). The results of a retrospective biomonitoring study (Wittassek et al. 2007a) indicate that the inner burden to DEHP has decreased during the last twenty years in Germany by a factor of nearly two.

Table 5. Daily DEHP intake estimations (µg/kg bw/d) deduced from urinary DEHP metabolite measurements

study	Country	Sampling year	n (age)	DEHP intake estimate Median	95th P
David (2000)[b]	USA	1988-1994	289 (20-60)	0.6[a]	3.1
Kohn (2000)[c]	USA	1988-1994	289 (20-60)	0.7	3.6
Koch (2003a)	Germany	2002	85 (7-63)	(13.8)[d] 4.6[e]	(52.1)[d] 17.0[e]
Wittassek (2007b)[f]	Germany	2001/2002	239 (2-14)	4.3[g] 7.8[h]	15.2[g] 25.2[h]
Wittassek (2007a)[i]	Germany	2001/2003	120 (20-29)	2.7	6.4

[a] Geometric Mean
[b] Values based on MEHP; metabolic factors adopted from Anderson et al. (2001)
[c] Values based on MEHP; metabolic factors adopted from Peck and Albro (1982)
[d] Values based on 5OH-MEHP and 5oxo-MEHP; metabolic factors from Schmid and Schlatter (1985)
[e] Values based on 5OH-MEHP and 5oxo-MEHP; applying metabolic urinary factors from Koch et al. (2005)
[f] Values based on MEHP, 5OH-MEHP and 5oxo-MEHP; applying metabolic urinary factors from Koch et al. (2005a)
[g] creatinine based evaluation
[h] volume based evaluation
[i] Values based on MEHP, 5OH-MEHP, 5oxo-MEHP, 2cx-MMHP and 5cx-MEPP; applying metabolic urinary factors from Koch et al. (2005a)

3.4.7. Exposure to DEHP following medical procedures

DEHP is currently the primary plasticizer used in PVC-containing medical devices such as containers for blood or nutrients, tubings and catheters. Thus patients undergoing medical treatment can be exposed to DEHP released from PVC medical devices (FDA 2002, Health Canada 2002). The following procedures which a potential for high exposure to DEHP are identified :

- Exchange transfusion in neonates
- ECMO in neonates
- Total Parenteral Nutrition (TPN) in neonates
- Multiple procedures in sick neonates
- Haemodialysis in peripubertal males
- Haemodialysis in pregnant or lactating women
- Enteral nutrition in neonates and adults
- Hearth transplantation or coronary artery bypass graft surgery
- Massive infusion of blood into trauma patient
- Transfusion in adult undergoing ECMO

Depending on the medical procedure exposure to DEHP varies widely and is a function of the lipophilicity of the fluid that comes into contact with the medical devices, the PVC surface size, the temperature, the flow rate and the contact time (Haishima et al. 2005, Hanawa et al. 2003, Hanawa et al. 2000, Kambia et al. 2003, Loff et al. 2002, Loff et al. 2000, Loff et al. 2004). Polyethylene linings of PVC articles (e.g. tubings) do not seem to substantially prevent the release of DEHP (Bourdeaux et al. 2004, Demore et al. 2002).

3.4.8. Adult exposure during medical procedures

Exposure to DEHP due to the usage of PVC medical devices can be short- or long-term. Long-term exposures in adults comprise haemodialysis, continuous ambulatory peritoneal dialysis (CAPD), transfusions of blood and blood products to patients with leukemia, aplastic anemia, sickle cell anemia, clotting disorders, administration of total parental nutrition

(TPN) and enteral nutrition of critically ill patients. Short-term DEHP exposures include blood transfusions e.g. in trauma patients, patients undergoing surgical procedures or extracorporeal membrane oxygenation (ECMO) procedures, and intravenous infusion of drugs.

Reported DEHP exposures estimated due to medical procedures for adults are summarized in Table 6. The reported data are based on measurements of DEHP blood levels in patients before and after specific medical procedures, area under curve (AUC) calculations and DEHP levels in stored blood and blood components together with different scenario assumptions (e.g. rate extraction of DEHP). Long-term haemodialysis is the continuously repeated procedure, which may result in the highest cumulative dose of DEHP (up to 2200 µg/kg/d). Blood transfusions to trauma patients or during ECMO may be the short-term procedure that gives the highest acute DEHP exposure in adults (up to 10 mg/kg/d).

Table 6. Daily DEHP exposure of adults due to medical procedures using PVC medical devices calculated from measurement of DEHP in patient's blood or calculated from the leaching rate of DEHP from the medical apparatus (Health Canada 2002)

Medical procedure	Daily DEHP dose (µg/kg/d)	Reference
Long-term exposures		
Haemodialysis	640[a,b,c] (150-2200)	Pollack (1985)
	450[a,b,c] (270-1210) - delivered dose 100[a,b,c] (20-360) - retained dose	Faouzi (1999)
	230[c] (50-850) - retained dose	Dine (2000)
Continuous ambulatory peritoneal dialysis	20[e]	Mettang (1996)
Long-term transfusion of blood and blood products	6-90[f]	Jacobson (1977) Doull (1999) Plonait (1993) Health Canada (2002)
Long-term total parenteral nutrition	130-280[d]	Mazur (1989) Loff (2000)
	800-2000 µg/day[d] (infants/children)	Kambia (2003)
Short-term exposures		
Transfusions of blood components		
Trauma patient	8500[f] (63 units whole blood) 1300-2600[b] (2.5l whole blood)	Jaeger and Rubin(1972)
During ECMO	3000-10000[f] (21-46 units combined blood products)	Sjoberg (1985b) Butch (1996)
Cardiopulmonary bypass		
During artificial heart transplant	2400[e]	Barry (1989)
IV Infusion of drugs		
Non-liphophilic drugs	< 5[f]	Health Canada (2002)
Lipophilic drugs	up to 1500[f]	Pearson (1993)

a assuming three dialysis sessions per week for a 70 kg patient
b area under curve (AUC) calculations
c estimated by DEHP blood levels coming to and/or from the patient, 4h-dialysis treatment
d based on estimated rates of DEHP extraction from PVC storage bags and infusion lines
e calculated from DEHP serum concentrations measured in patients
f based on DEHP concentrations in stored blood and blood components or infusion solutions

The estimated DEHP doses given in Table 6 are based on measurements of DEHP itself. However, analytical determination of DEHP is prone to contamination during sample handling and processing. This is to be kept in mind when assessing the DEHP exposure levels estimated.

Patients receiving blood and blood products are not only exposed to DEHP but also to its hydrolysis product, mono(2-ethylhexyl) phthalate (MEHP), which is formed by plasma lipases (Albro and Thomas 1973, Peck et al. 1979). The conversion has been shown to increase with increasing storage time and temperature, while storage at low temperatures prevent it (Cole et al. 1981, Rock et al. 1978). MEHP has been measured in stored blood, blood products and peritoneal dialysate (Cole et al. 1981, Labow et al. 1986, Peck et al. 1979, Rock et al. 1978, Sjoberg et al. 1985a, Sjoberg et al. 1985b). Nevertheless, the data available are not sufficient to accurately calculate the in vitro conversion rates (Health Canada 2002). The MEHP exposure due to exchange transfusion has been estimated to be in the range of 5 to 680 µg/kg/d (Sjoberg et al. 1985a, Sjoberg et al. 1985b).

Exposure to DEHP can also occur through voluntary medical treatments such as apheresis procedure to donate blood products (Table 7). Many disposables used in apheresis are manufactured from PVC containing DEHP. Highest DEHP exposure has been estimated for continuous-flow plateletpheresis (dual needle technique). Based on urinary measurements of DEHP metabolites Koch et al. (2005b) calculated for such donors (overall) daily DEHP intakes of 28.2-38.1 µg/kg/d. For platelet donors undergoing the single needle discontinuous-flow technique values were some lower with 14-24 µg/kg/d. The internal burden after plasma donation (3.1-9.6 µg/kg/d) was not elevated in comparison to controls (3-11.6 µg/kg/d), which indicates that the DEHP dose associated with plasmapheresis is not elevated above background. This may be because the lipid-rich plasma may contain most of the DEHP, which is removed from the body by the procedure. Buchta et al. (2003) estimated from serum DEHP concentrations exposures of 1.8-20.3 µg/kg/d due to apheresis procedure.

Table 7. Daily DEHP exposure of adults due to apheresis procedure using PVC medical devices calculated from measurement of urinary DEHP metabolites (Koch 2005b, Koch 2005c) or from serum DEHP concentrations (Buchta 2003)

Donation procedure (apheresis technology used)	n	Mean daily DEHP dose (range) [µg/kg/d]	Reference
Controls	5	6.2 (3.0-11.6)	Koch 2005b
Plasma	6	5.7 (3.1-9.6)	
Platelet (discontinuous)	6	18.1 (14.3-23.8)	
Platelet (continuous)	6	32.3 (28.2-38.1)	
Platelet (continuous)	1	31.6	Koch 2005c
Platelet (discontinuous)	19	6.5 (1.8-20.3)	Buchta 2003
Platelet (continuous)	17	7.2 (2.0-20.3)	

3.4.9. Newborns at risk

Developing foetus and the neonate represent the most vulnerable phases of life particularly with regard to developmental and reproductive toxicity. In particular, neonates in the Neonatal Intensive Care Unit (NICU) environment, due to their small body size, their physical condition and multiple medical device-related DEHP exposure (feeding tubes, infusion tubing systems, umbilical catheters, PVC blood bags, transfusion tubing systems, hemodialysis systems, cardiopulmonary bypass, continuous peritoneal dialysis, extracorporeal membrane oxygenation circuits or endotracheal tubes) combined with their developmental vulnerability represent a population at particularly increased risk (CERHR 2005, FDA 2002, Health Canada 2002).

In fact, neonates receive higher doses, in terms of body weight, of DEHP than the general population (Calafat et al. 2004b, Green et al. 2005) and their daily dose to DEHP may increase up to 20 folds the tolerable daily intake (Jaeger et al. 2005). The combination of prenatal and postnatal exposures may exacerbate the reproductive hazard. Therefore a concern was raised about potential health effects of DEHP (CERHR 2005, ECB 2004). Accordingly research into alternatives to DEHP-containing medical devices that may come in contact with human tissues was suggested (Jaeger et al. 2005). In addition, further studies are needed to evaluate if less invasive medical treatments may reduce phthalate exposure risk (Latini et al. 2003b).

Table 8 gives estimates of DEHP exposures in neonates resulting from medical treatments calculated from spot measurements of DEHP or delivered doses using AUC calculations. The values are related to a 4 kg infant. However, most newborns requiring medical intensive care are premature born babies who weight significantly lighter, in general between 500 and 2500 g. Therefore, the DEHP exposure in relation to body weight may even be higher in premature newborns. The DEHP exposure estimates reach for many procedures the mg/kg range. Compared to adults undergoing the same medical procedures the values are significantly higher and are several orders of magnitude above the exposure levels estimated for the general population. The highest short-term exposure may occur due to double volume exchange transfusion (up to 23 mg/kg/d) while ECMO is the medical treatment, which may give the highest daily exposure over a prolonged period of time (up to 14 mg/kg/day). Moreover, critically ill neonates generally require not only a single medical treatment but also a combination of several medical interventions, which may lead to even much higher DEHP exposure. The FDA (2002) has estimated an upper-bound daily DEHP dose on the order of 3 mg/kg/d for a newborn (4 kg) in the neonate intensive care unit (NICU) setting considering exposure from multiple devices. Such exposures may occur for a period of weeks or even months. However, the total DEHP exposure may vary dramatically from medical centre to centre, depending on the treatment protocols and specific medical devices used (Rosenberg et al. 1994).

Table 8. Estimated dose of DEHP received by neonates undergoing medical procedures calculated from measurement of DEHP in patient's blood or calculated from the leaching rate of DEHP from the medical apparatus (Health Canada 2002)

Medical procedure	Daily DEHP dose (µg/kg/d) of neonate (4 kg)	Reference
Infusion of pharmaceuticals		Loff (2000)
• Midazolam (24 ml)	7 a	
• Fentanyl (29 ml)	33 a	
• Propofol (1%, 10 ml, 24h)	1640 a	
TPN	30 (free of lipid) a	Loff (2000)
	2500 (lipid emulsion 20%, 27°C)	Loff (2002)
	3250 (fat infusion, 33°C) a	
Exchange transfusion – short term	1200-22600 [c]	Plonait (1993)
	840-3300 [b]	Sjoberg (1985a)
	1700-4200 [a]	Sjoberg (1985b)
Single dose Packed Red Blood Cells (20 ml)	36-152 [a]	Loff (2000)
	232 [a]	
Single dose Platelet-Rich Plasma (20 ml)	138-2020 [a]	
Single dose Fresh Frozen Plasma (20 ml)		
ECMO - sub-acute	Up to 14,000 [d] (14000 µg/kg/ 10 days)	Schneider (1989)
	0 (heparin coated PVC tubing)	Karle (1997)
	Up to 3,490 [e] (34900 µg/kg/ 10 days)	
Respiratory therapy - oxygen therapy	< 130 [f]	Health Canada 2002
Respiratory therapy using endotracheal tube	< 700 [f]	Health Canada 2002 Latini 1999
Aggregate exposures of NICU infants (iv administration of sedatives, TPN, replacement transfusion)	2830	FDA (2002)

a calculated from DEHP concentrations in the respective medium
b AUC calculations
c DEHP blood levels measured before and after medical procedure
d based on blood levels and certain assumption
e based on blood levels and in vitro leaching rates measured
f calculated from DEHP vapour pressure

The urinary concentrations of DEHP metabolites in neonates undergoing intensive medical interventions have been found to vary widely and reach levels that are much higher than those found in the general population (Table 9). Compared to adults the ratios among the metabolites are shifted in favour of the oxidative metabolites with 5cx-MEPP being the main metabolite (Calafat et al. 2004a, Koch et al. 2006).

Table 9. Median (95th percentile) DEHP metabolite levels in µg/l measured in urine of infants undergoing intensive medical interventions

Reference	N	Birth weight ± SD [g]	5cx-MEPP	5OH-MEHP	5oxo-MEHP	2cx-MMHP	MEHP
Calafat 2004a [a]	6	666 ± 167	n.d.	2221 (13161)	1697 (10413)	n.d.	129 (704)
Green 2005 [b], Weuve 2006	13 24 17	n.s.	n.d.	low: 27 medium: 307 high: 555	low: 29 medium: 286 high: 598	n.d.	low: 4 medium: 28 high: 86
Koch 2006 [c]	45	1976 ± 714	293 (5500)	41.6 (557)	34.8 (406)	8.3 (129)	-

[a] results of 41 urine samples of premature newborns ; intensive care interventions for more than 2 weeks
[b] DEHP exposure was rated low, medium or high based on the kind of medical devices used
[c] premature neonates treated with various medical procedures
n.d.: not determined
n.s.: not specified

Based on the urinary measurements Koch (2006) estimated for 45 premature neonates a median daily DEHP dose of 42 µg/kg bw/d and a 95th percentile of 1780 µg/kg bw/d. The large difference between the median and the 95th percentile indicate a great variability in DEHP exposure for newborns in intensive care, which may reflect the variety and intensity of the medical procedures performed. The maximum estimated daily DEHP intake was 2300 µg/kg bw/d, which is separated from the NOAEL (4.8 mg/kg bw/d) for testicular and developmental toxicity in rats only by a factor of two (Wolfe and Layton 2003). Based on the data of Calafat et al. (2004a) even higher maximal DEHP exposures up to 6000 µg/kg bw/d have been estimated well above the NOAEL observed in the rat study (CERHR 2005).

3.4.10. Summary on the exposure to DEHP

The general population is exposed to DEHP through a variety of routes with food being the primary source. Several metabolite excretion studies suggest exposure to DEHP in the whole general population. In general, DEHP exposure assessments from probabilistic calculations from DEHP measurements in environmental media and dose reconstructions from urinary metabolite levels agree within an order of magnitude. Most recent studies suggest a current median exposure of 2 to 5 µg/kg bw/day, whereas the 95th percentile is estimated to be between 6 and 17 µg/kg bw/day. Children may have somewhat higher body burden of DEHP than adults. There are indications that exposure to DEHP in the general population has decreased during the last years.

Medical procedures using PVC medical devices can lead to DEHP exposures much higher than the background levels. However, the extent of exposure largely depends upon the medical treatments given and the duration of the treatment. In adults, highest doses of DEHP may result by transfusions of blood components reaching up to several mg/kg bw/day. It has been shown that also voluntary medical treatments such as apheresis procedure to donate blood products can cause significant exposure to DEHP. For adults the extent of exposure varies depending on medical procedures conducted. For some treatments the mg/kg bw/day range may easily be reached. For blood transfusion procedures peak values up to 22 mg/kg bw/day have been estimated. Premature neonates in intensive care units, being dependent on multiple medical procedures, can receive even higher DEHP exposures than adults relative to their kg bw. These exposures may be in the same range as the doses inducing reproductive toxicity in animal studies.

3.4.11. Toxicity

Comprehensive reports have been issued recently which provide in depth evaluations of the toxicity of DEHP, in particular, the European Union Risk Assessment Report of 2006 (draft version, an update of the final report published in 2004 in the framework of the Existing Chemicals program at http://ecb.jrc.it) and the NTP-CERHR Expert Panel Update on the Reproductive and Developmental Toxicity published in 2006 (available http://cerhr.niehs.nih.gov). SCENIHR has carefully considered these summary documents along with new pertinent original publications.

3.4.12. Animal Studies

Acute toxicity

Acute toxicity studies of good quality indicate low acute toxicity of DEHP, with an LD_{50} of >25 g/kg in rats and mice. The intravenous acute toxicity of DEHP is higher, with an LD_{50} in the region of 200-250 mg/kg in rats. The acute toxicity of MEHP is about five times higher than that of DEHP (ECB 2006, NTP-CEHRHR, 2005).

Repeated dose toxicity

Numerous studies investigated the toxicity of DEHP upon short-term and repeated administration to experimental animals, mostly rats and with application by the oral route. Many of these studies are comparable to guideline studies and conducted in conformity with GLP. Target organs for DEHP induced toxicity in rodents were kidney, liver and testis.

The effects on the kidneys included increased absolute and relative organ weights, increased incidence and severity of mineralization of the renal papilla, increased incidence and/or severity of tubule cell pigment, and increased incidence and/or severity of chronic progressive nephropathy. In long-term studies in rats and mice, there was no indication that DEHP-related changes in the kidney were reversible upon cessation of DEHP-exposure. The lowest NOAEL for kidney toxicity is 500 mg/kg DEHP in the feed (corresponding to 28.9 mg/kg/day in the males and 36.1 mg/kg/day in the females) derived from a well-performed 104-week-study in rats (Moore 1996, David et al. 2000a) and based on increased absolute and relative kidney weight in both sexes at the next higher dose level (LOAEL = 146.6 mg/kg bw/day). More severe kidney lesions were observed at the highest dose level.

The most striking effects observed in the liver are hepatomegaly due to hepatocyte proliferation (characterised by increased replicative DNA synthesis/cell division and hypertrophy), peroxisome proliferation, and hepatocellular tumours. The effects on the liver (hepatomegaly) are apparently mediated by peroxisome-proliferator activated receptor (PPARα) and agonistic interaction of DEHP and its metabolite MEHP with the receptor. There are, however, marked species differences in the PPARα-mediated effects of DEHP, such that the hepatotoxic effects of DEHP in rodents are not judged to be relevant for humans (IARC, 2000).

In repeated exposure study 16 rats were pretreated with 100 mg/m^3 for 2 weeks (aerosol) 6 hours per day, 5 days per week. The study indicates that following repeated inhalation exposure long term retention does not occur. There are no other relevant studies in rodents investigating the health effects in the respiratory tract.

Genotoxicity/mutagenicity

DEHP has been studied extensively in a wide range of *in vitro* and *in vivo* assays for detection of gene mutations, DNA damage, and chromosomal effects. Most of the studies are performed according to GLP principles and are comparable to guideline studies for mutagenicity or genotoxicity. The results have been negative in the majority of assays with DEHP and metabolites (MEHP and 2-EH). Positive results were obtained in assays on cell transformation, induction of aneuploidy, and cell proliferation. However, these test systems are also sensitive to several non-genotoxic substances such as tumour promoters and/or peroxisome proliferators. Thus, in conclusion, DEHP and its major metabolites are considered to be non-mutagenic substances.

Carcinogenicity

Several studies on the carcinogenicity (and mechanisms of carcinogenicity) of DEHP have been performed in rats and mice with oral administration, and an inhalation study in Syrian golden hamsters. These studies are summarized in the RAR report of 2006 and other summary documents (IARC, 2000).

The results of four different peroral long-term carcinogenicity studies in rats and mice indicate clearly that DEHP is a hepatocarcinogen in both males and females of the two species. In the NTP studies (1982a), the LOAEL for tumour induction in mice was 3000 mg/kg DEHP in the feed (670 mg/kg bw per day for male mice). A NOAEL for DEHP-induced tumour development in the rat has not been identified as the lowest dose in the study resulted in an increase of the incidence of liver tumours. The LOAEL for tumour induction in rat was 6000 mg/kg DEHP in the feed (320 mg/kg bw per day for male rats). Two more long-term carcinogenicity studies in rats and mice have been conducted by Moore (1996, 1997) and reported by David et al. (2000a and 2000b). An overall NOAEL for the tumour induction and for the effects on the liver, kidney and testis was established as 500 mg/kg DEHP in feed (29 mg/kg bw/day for male rats). The LOAEL and the NOAEL for tumour induction (male mice with hepatocellular neoplasms) in this study was 1500 and 500 mg/kg DEHP in the feed, respectively (corresponding to 292 and 98 mg/kg bw per day for males of the two dose groups respectively). The LOAEL and the NOAEL for non-neoplastic effects on the liver in this study were 500 and 100 ppm DEHP in the diet, respectively (98 and 19 mg/kg bw per day for males of the two dose groups respectively). Marked species differences with respect to hepatic response to peroxisome proliferation are apparent. Rat and mice seem to exhibit the highest sensitivity. Guinea pigs and monkeys are relatively insensitive. In marmosets, the liver weight was not affected and a slight increased activity of peroxonal enzymes was observed following administration of 2000 mg/kg bw for 14 days.

In conclusion: DEHP was found to induce liver tumors in rats and mice mainly by the activation of the PPARα receptor, a mechanism considered not to be relevant in the human liver.

Immunotoxicity

Larsen and colleagues (2001a, 2001b) studied adjuvant effects of DEHP, and MEHP and other phthalate monoesters in a subcutaneous injection model in BALB/c mice. Ovalbumin (OVA) was used as the model antigen and ovalbumin-specific IgE, IgG_1, and IgG_{2a} antibodies were measured as indicators of allergic response. MEHP produced a significant increase in both IgE and IgG_1 levels, and DEHP increased IgG_1 levels, these antibodies being related to a Th_2 response predominant in Type I allergy. The adjuvant activity was noted when DEHP was mixed with the antigen ovalbumin, When a mixture of DEHP and ovalbumin was administered intraperitoneally in PPAR-alpha knock out mice OVA specific IgE, IgG1 and IgG2a responses were similar to responses in the wild type mouse strain indicating that the adjuvant activity of DEHP is mediated by a PPAR-alpha receptor independent mechanism (Larsen and Nielsen 2007). Airborne exposure to DEHP and OVA only induced an increase in serum IgG1 and inflammatory cells in the lung, but only at rather high concentrations of 13 mg/m^3. Lower DEHP airborne exposure comparable to levels measured in ambient air did not show an adjuvant effect or induced allergic lung inflammation in the mouse model used (Larsen et al 2007). Similar results were obtained for the DEHP metabolite MEHP, so it was speculated whether the airway effects of DEHP are mediated by MEHP (Larsen et al 2007, Hansen et al. 2007). Although the induction of antigen (OVA) specific IgG1 antibodies is an indicator for immunogenicity and adjuvancy in mouse experimental systems, it is not clear whether this response should be considerd a protective or a risk factor for the development of IgE and thus immediate type hypersensitivity (Larsen et al 2007). For some other routes and combinations of DEHP (topical) and OVA (subcutaneous) administration no effect on anti-OVA antibody production was noted (Dearman et al. 2008).

In a model for atopic dermatitis also the combined intraperitoneal administration of DEHP and antigen was found to exacerbate skin responses to the antigen (Takano et al 2006).

One of the metabolites of DEHP, MEHP (monoethylhexyl phthalate) induced immunosuppression, i.e. reduced antibody titres, when the same protocol was used (Larsen et al. 2001b), indicating that DEHP and its metabolites have the potential to interact with the immune system in various ways, although it is unknown whether such effects are observed in humans after oral or parenteral exposition to DEHP.

Some monophthalates have been shown to promote cytokine IL-6 and IL-8 production in the human epithelial cell line A549, indicating a potential role in inflammatory process (Jepsen et al. 2004).

In conclusion, DEHP was found in experimental systems to have the potential to interact with the immune system depending on the actual exposure conditions.

Reproductive toxicity

The reproductive or developmental toxicity of DEHP have been studied in rats, mice, hamsters, ferrets and marmosets. Based on the available data, which varies in both study designs and number of animals included, testicular effects have been demonstrated in both male rodents and non-rodents. The testis toxicity of DEHP is age dependent (Sjoberg et al. 1985b). The lowest NOAEL is seen in the range from 3.5 to 4.8 mg/kg b.w. in rats. The females need to be exposed in the most critical period of 12-21 days during pregnancy to see testicular effects at low doses (< 10 mg/kg bw) (Fabjan et al. 2006). In mice, after continuous exposure during breeding a NOAEL for maternal developmental toxicity of 600 and 20 mg/kg bw/day can be identified. In ferrets a LOAEL is 1200 mg/kg bw/day (Lake 1976). In animal experiments DEHP is embryotoxic and causes malformations in mice but not in rats when given orally in doses close to the maternal toxic dose (Sullivan et al. 1993).

For male reproductive toxicity caused by DEHP there is a difference in sensitivity between various animal species, rodents being more susceptible than non human primates (Rhodes et al 1986). The same dose (2000 mg/kg for 14 days orally) induced testis atrophy and liver enlargement in rats, but failed to do so in marmosets (Rhodes et al. 1986). Also in another study, adult male marmosets treated up to 2500 mg/kg DEHP for 13 weeks failed to show evidence of testicular toxicity (Kurata et al. 1998). After short term exposure of young adult cynomolgus monkeys for 14 days to di-isonyl phthalate (DINP) or DEHP at 500 mg/kg daily, there were no treatment related effects observed for liver, kidney and testis (Pugh et al. 2000). In addition, when marmoset monkeys were exposed to high doses of DEHP up to 2500 mg/kg daily for 65 weeks, no changes were noted in the testis (Tomonari et al 2006). In this study the animals were exposed continuously in the pre-adolescent period starting at approximately day 100 after birth until the peri-adolescent period at the age of almost 18 months. So, in studies using marmosets and cynomolgus monkeys no effect on testicular function was observed after high DEHP exposure. These observations are of importance for extrapolation to humans as for spermatogenesis the marmoset was found to have similarities to the human, and it was concluded to be a suitable model for studies relevant for human testicular function (Millar et al. 2000).

In a previous CSTEE opinion (CSTEE, 1998), testicular toxicity was identified as the critical endpoint for DEHP from a 13-week dietary study in Sprague-Dawley rats, and a NOAEL was set at 3.7 mg/kg bw/day based on mild Sertoli cell vacuolation (Poon et al. 1997). Since that time, the result of a new multigenerational reproductive toxicity study of DEHP in Sprague-Dawley rats has become available (Wolfe and Layton 2003). The ECB 2006 evaluated the study in which three generations were fed DEHP in the diet corresponding to doses of 0.1, 0.5, 1.5, 4.8 14, 46, 359 and 775 mg/kg bw/day. There were dose-dependent effects on numerous testis related parameters (decreased testicular weight, small or aplastic testes, seminiferous tubular atrophy, infertility at high doses) The NOAEL for both testicular toxicity and developmental toxicity from this experiment was determined at 4.8 mg/kg bw/day.

The CSTEE agreed with the RAR to use this NOAEL rather than 3.7 mg/kg bw/day from the study of Poon et al. (1997), since the endpoints seen in the Wolfe and Layton (2003) study are more robust and the study was well performed (CSTEE 2004).

According to Council Directive 67/548/EEC, DEHP is classified Toxic, and with effects on male and female fertility Category 2, R 60 and for developmental toxicity in category 2, R61.

3.4.13. Mechanisms of Action of DEHP

In general three mechanisms have been proposed to account for liver carcinogenicity

- Hepatomegaly and peroxisome proliferation leading to oxidative stress and generation of electrophilic free radicals
- Increased hepatocyte proliferation/suppression of hepatocellular apoptosis and
- Activation of peroxisome proliferators-activated receptors (PPARs).

Still the understanding of the mechanism of action in the liver is not clarified.

The effect of DEHP on liver cells has been studied in details and the peroxisome proliferators are involved in the hepatotoxicity of DEHP. PPARs play a number of important roles in normal physiology and play a role as a modulator of signal molecules that mediate changes in gene expression to maintain lipid homeostasis (Rusyn et al. 2006).

The mechanisms of the toxic effect of DEHP on the male reproductive organ have been investigated in several animal studies. Also in the testis peroxisome proliferators-activated receptors PPAR and their subtypes are now in focus to explain some of the reproductive effects of phthalates. The alpha and beta subtypes are expressed in adult rat testis, as well as in neonatal and adult Sertoli and Leydig cells although the literature shows significant discordance in results to explain the role of PPAR (Corton and Lapinski 2005, Latini et al. 2006).

The antiandrogenic effects of some phthalates have been suggested to be due to reduced androgen availability in target organs causing malformations of male reproductive organs and low adult sperm counts (Gray et al. 2000, Barlow et al. 2003). Maternal DEHP treatment from gestational day 14 to postnatal day 3 resulted in reduced testosterone synthesis to female levels (Parks et al. 2000). In addition, in contrast to the antiandrogen effect in vivo, DEHP and its metabolite MEHP did not show an affinity for the human androgen receptor in an in vitro assay. These results indicate that DEHP has an effect on rat male development by reducing the testosterone levels in the foetal male during a critical stage of reproductive tract differentiation (Parks et al. 2000). The phthalates with side-chain length C4 to C6 produce similar severe reproductive effects in experimental animals. Steroidogenesis in foetal rats is reduced by DEHP *ex vivo* and DINP, DBP, DIBP, and DEHP seem to reduce testicular testosterone production by a similar mechanism of action (Barlow and Foster 2003, Borch et al. 2004, Borch et al. 2006). In addition, plasma LH levels in male foetuses were elevated (Borch et al. 2004). Immunohistochemistry showed a clear reduction in the nuclear receptor steroidogenic factor-1 (SF-1) and peroxisome proliferator PPAR gamma after gavage administration of 300 mg/kg bw/day DEHP (Borch et al. 2006b). Phthalates are PPAR agonists and have been found to reduce testosterone production in primary Leydig cell culture and in adult rats (Corton and Lapinski 2005).

In mice there is a study that demonstrates the same spectrum of developmental toxicity in normal mice and mice that were genetically incapable of expressing peroxisome proliferation due to lack of PPAR-alfa indicating a role for the direct toxicity (ECB 2006 in press). In laboratory animals the metabolites are less studied but one report suggests that at least in rats the antiandrogenic effect is partly caused by 2 antiandrogenic metabolites 5OXO-MEHP and 5-OH-MEHP (Stroheker et al. 2005).

In adult or prepubertal rats, other mechanisms of action than PPARs activation may be of importance. In the rat testis the Sertoli cell may be the target for acute toxicity after exposure to high doses of DEHP. In Sertoli cells, it has been shown that the cell structure protein vimentin and an increased caspase-3 level activity, appear to be sensitive and early markers of MEHP testis toxicity at 6 hours after one application of 400 mg/kg bw by gavage (Dalgaard et al. 2001). The same effect of DEHP after oral doses of 5 and 10 g/kg bw for 4 weeks resulted in collapse of vimentin in the Sertoli cells (Dalgaard et al. 2000).

Little is known about the mechanism of action in humans. However, DEHP is able to induce in animals all the malformations, which are present in the so called testicular dysgenesis syndrome. The testicular dysgenesis syndrome includes the following human male reproductive disorders, cryptorchidism and hypospadias in babies or testis cancer and low sperm counts in young men. It has been proposed that maldevelopment (dysgenesis) of the foetal testis results in hormonal malfunction or other malfunctions of the testicular somatic cells eventually leading to the malformations as part of the testicular dysgenesis syndrome (Sharpe & Skakkebaek 2003).

In humans most information of DEHP exposure is obtained by measuring of the DEHP metabolites in urine (Koch et al. 2005a). However, the role of the metabolites in inducing toxic effects or possible mechanism of action is not well known. It may be assumed that the half-life of these metabolites may play a role in their ultimate toxic effects. In laboratory animals the metabolites are less studied but some studies determining DEHP metabolites suggests that at least in rats the antiandrogenic effect of DEHP is partly caused by 2 antiandrogenic metabolites, namely 5oxo-MEHP and 5OH-MEHP (Stroheker et al. 2005).

3.4.14. Evidence from epidemiological studies

Potential male developmental effects in humans include hypospadias, cryptorchism and decreased anogenital distance which are part of the so-called testicular dysgenesis syndrome. There is limited epidemiologic evidence of the effects of phthalates on these health outcomes.

Hypospadias and cryptorchism.

Van Tongeren and colleagues (2002) developed a job-exposure matrix (JEM) to assess exposure to potential endocrine disrupting agents, including phthalates. Vrijheid and colleagues (2003) applied this JEM in a study of 3471 hypospadias cases identified from the National Congenital Anomaly System of England and Wales in 1980-1996, which included a total of 35962 cases of congenital anomalies. The authors compared the prenatal exposures of hypospadias cases with exposures of all the cases. The risk of hypospadias was not related to estimated maternal occupational exposure to phthalates. For 1992-96 there was an increased risk of hypospadias related to probable exposure, mainly among hairdressers, with an adjusted odds ratio of 1.52 (1.05-2.20) without social class adjustment, and 1.26 (0.81-1.97) after such adjustment. The JEM was also applied in a Dutch nested case-control study of 56 cases of hypospadias and 78 cases of cryptorchism and 313 controls selected from a cohort of 8,698 male newborns. No association was found between estimated occupational exposure to potential endocrine disrupting agents and these outcomes (Pierik et al. 2004). In a study on contamination of breast milk with phthalates no association was found between breast milk phthalate monoester levels and cryptorchidism, but other potential anti-androgenic metabolites were not measured (Main et al. 2006).

Decreased anogenital distance

Swan et al. (2005) provided the first indications for the effects of phthalates on anogenital distance in a study of 134 male infants. Eighty five of the participating pregnant women gave a prenatal urine sample, which was analysed for nine phthalate metabolites commonly used as biomarkers of exposure to phthalates. Anogenital distance was measured after the delivery. For the 9 urinary metabolites measured, including monomethyl phthalate, monoethyl phthalate, mono-n-butyl phthalate, mono-iso-butyl phthalate, monobenzyl phthalate, mono-3-carboxypropyl phthalate, mono-2-ethyl-5-hydroxyhexyl phthalate, mono-2-ethylhexyl phthalate, mono-2-ethyl-5-oxohexyl phthalate. Four of these were associated with anogenital index (AGI=anogenital distance/kg bw), being monoethyl phthalate, mono-n-butyl phthalate, monobenzyl phthalate and mono-iso-butyl phthalate. Boys with a reduced anogenital index (AGI) may have an increased likelihood of impaired testicular descent, penile volume and scrotal size, although in the study itself, no diseases or malformations were identified. However, the data were considered insufficient as solid evidence for an effect and need further elaborations with larger studies, but do add to the concern for male reproductive effects (Kaiser 2005, Sharpe 2005).

Birth weight and gestational age

Latini and colleagues (2003a) measured serum DEHP and MEHP concentrations in the cord blood of 84 consecutive newborns. Detectable cord blood pthtalates concentrations were found in almost 90 % of these individuals. In this single study the mean gestational age was significantly lower among newborns with detectable cord blood MEHP compared with those without (38.2 vs. 39.4 weeks). Also the mean birth weight was lower (3,150 vs. 3475 g) although the difference was not statistically significant. In logistic regression analysis adjusting for potential confounders, the absence of MEHP was a significant determinant of gestational age. This study suggests a possible effect of DEHP on pregnancy outcome.

Pubertal development

Two studies have investigated associations between pubertal development and phthalate exposure (Colon et al. 2000, Rais-Bahrami et al. 2004). The relation between serum phthalate concentrations and premature breast development was studied in a case-control study of 41 patients from the San Juan City Hospital Pediatric Endocrinology Division and 35 controls from the general pediatric care who did not have signs of premature sexual development (Colon et al. 2000). Higher serum levels of DMP, DEP, DBP, and DEHP plus its metabolite MEHP were measured in cases than controls. The average concentration of DEHP was 450 ppb in cases and 70 ppb in controls, the difference being statistically significant. This was not seen with other phthalates studied. There appears to be a correlation between DEHP exposure and breast development in young females. However, the quality of the data is uncertain due to laboratory and/or diagnostic procedures performed (CERHR 2005).

Rais-Bahrami et al. 2004 reported a 14-16 years follow-up study to DEHP toxicity noted in adolescents after a high DEHP exposure as neonates during extracorporeal membrane oxygenation (ECMO) support. The onset of puberty and sexual maturity was evaluated in 19 adolescents (13 males and 6 females). The results showed that there were no significant adverse effects on their physical growth and pubertal maturity. Thyroid, liver, renal and male and female gonadal functions tested were within normal range for age and sex distribution. It was suggested that the acute and short term exposure to DEHP by the intravenous route, and a lack of conversion of DEHP to MEHP may be protective against its long term adverse effects (Rais-Bahrami et al. 2004). A limitation of the study is the low number of individuals studied and the evaluation period of maximal 16 years.

In a 20 year follow up study Hack et al. 2002 compared young adults with a normal birth weight (mean 3279 gram, n=233) to very low birth weight (mean 1179 gram, n=242) individuals, assumed to have had a high DEHP exposure. The very low birth weight individuals showed educational disadvantages persisting into early adulthood. There were no differences observed concerning male fertility.

Endometriosis

Two case-control studies have investigated the relations between biomarkers of DEHP exposure and the risk of endometriosis. A case-control study of Cobellis and colleagues (2003) provided first evidence of an association between plasma and peritoneal fluid levels of DEHP and the risk of endometriosis. The 24 cases were patients who underwent diagnostic laparoscopy for ovarian cysts or chronic pelvic pain and dysmenorrhoea and who had a histological confirmation of endometriosis. The 35 controls were healthy age matched individuals without infertility or reproductive diseases. The cases had a higher plasma concentration of DEHP (median 0.57 µg/ml, interquartile range 0.06-1.23) than the controls (0.18 µg/ml 0-0.44, P=0.0047), but the plasma MEHP and peritoneal DEHP and MEHP concentrations were similar. However, certain limitations in these studies include possible exposure due to medical procedures, information on the selection of controls, evaluation of confounding factors, and small sample size (CERHR Expert Panel 2005).

Reddy and colleagues (2006a) conducted a case-control study with 49 infertile women with endometriosis and two control groups. The first control group (I) included 38 age-matched women without endometriosis but with infertility related to tubal defects, fibroids, polycystic ovaries, idiopathic infertility and pelvic inflammatory disease diagnosed by laparoscopy. The second control group (II) comprised 21 age-matched fertile women undergoing laparoscopic sterilisation. The endometriosis cases had a significantly higher concentration of DBP (mean 0.44 µg/ml, SD 0.41), BBP (0.66, 0.61), di-n-octyl phthalate (DOP)_ (3.32, 2.17) and DEHP (2.44, 2.17) compared with both the first (DBP 0.08, 0.14; BBP 0.12, 0.20; DOP 0; DEHP 0.50, 0.80) and second control group (DBP 0.15, 0.21; BBP 0.11, 0.22; DOP 0; DEHP 0.45, 0.68). These studies indicate a correlation between the phthalate ester concentrations and the severity of endometriosis for all compounds.

Gonadal hormones and semen quality

Phthalate monoesters including MEHP, the initial metabolite of DEHP, and MBP are known testicular toxicant in rodents. The balance of gonadotropin and gonadal hormones is an important indicator of male fertility (see 3.4.5.2).

Main and colleagues (2006) studied 62 cryptorchid boys and 68 healthy boys from a prospective cohort of Danish and Finnish boys. As biomarkers of exposure, they analysed breast milk samples collected 1-3 months postnatally for phthalate monoesters including MMP, MEP, MBP, MBzP, MEHP, and MINP. Serum samples were analysed for gonadotropins, sex-hormone binding globulin (SHBG), testosterone, and inhibin B. No association was found between phthalate monoesters and cryptorchidism. MEP and MBP were positively, but weakly correlated with SHBG (Spearman correlation coefficient [r]=0.323, p=0.002 and r=0.272, p=0.01 respectively). MMP, MBBEP, and MBP were correlated with LH: free testosterone ratio and MINP with LH (r=0.243, p=0.019). MBP was negatively correlated with free testosterone (r=-0.22, p=0.033). These findings suggest some phthalates may have adverse effects on human Leydig cell development and function, which may be related to incomplete virilization in infant boys exposed to phthalates.

Pan et al. (2006) reported the effect of occupational exposures to high levels of the phthalate esters, DBP and DEHP on the balance of gonadotropin and gonadal hormones including the circulating concentration and/or balance of free testosterone (fT), luteunizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol (E2). They compared blood and urine concentrations of 74 male workers in a factory producing unfoamed polyvinyl chloride flooring and 63 men from a construction company matched for age and smoking status. The exposed workers had significantly elevated urinary concentrations of MBP (644.3 vs. 129.6 µg/g creatinine, $p < 0.001$) and MEHP (565.7 vs. 5.7 µg/g creatinine, $p < 0.001$). The fT concentration was significantly lower (8.4 vs. 9.7 µg/g creatinine. $P=0.019$) in the exposed workers compared with the unexposed. Among the exposed, fT had a negative correlation with MBP ($r=-0.25$, $p=0.03$) and MEHP ($r=-0.19$, $p=0.095$). In the regression analysis fT decreased significantly with increasing total phthalate ester score.

Duty et al. (2003a, 2003b, 2004, 2005) and Hauser et al. (2006) conducted a series of studies in male partners of subfertile couples recruited at an infertility clinic (US). They estimated associations between blood and urinary biomarkers of exposure to phthalates and various measures of semen quality and morphology. Sperm concentration, motility and motion parameters were measured using computing aided sperm analysis. Sperm DNA damage was measured using neutral comet assay. In an analysis of 168 males (Duty et al. 2003b), there was an exposure-response relation between MBP levels and sperm motility and concentration. Monobutyl benzyl phthalate (MBBP) levels were inversely associated with sperm concentration.

Hauser et al. (2006) studied 463 male partners of subfertile couples (including the 168 men in the previous study) who presented semen analysis at the infertility clinic. They compared urine concentrations of phthalates esters between 76 men with compromised sperm concentrations (<20 million/mL), 221 men with compromised sperm motility (<50% motile) and 114 with compromised morphology (<4% normal) with 210 subjects whose sperm concentration, motility and morphology was normal (above the three cut points). There was a dose-response relation between MBP and low sperm concentration (adjusted odds ratios per quartile: 1.00; 3.1; 2.5; 3.3, P for trend = 0.04) and suggestive evidence for a dose-response relation between MBzP and low sperm concentration (adjusted odds ratios per quartile: 1.00; 1.1; 1.1; 1.9, P for trend = 0.13). No association was found between monoethyl phthalate, monomethyl phthalate and the DEHP metabolites and the three semen parameters.

In an analysis of 220 males, straight-line velocity (VSL), curvilinear velocity (VCL) and linearity (VCL/VCL) of sperm motion were inversely associated with levels of MBP, MBzP, and MEHP (Duty et al. 2004). The association between urinary concentration of phthalate metabolites and sperm DNA damage was reported in two analyses with partly same study subjects (Duty et al. 2005, Hauser et al. 2006). Various measures of sperm DNA damage were measured, including comet extent and tail distributed moment. The studied metabolites were MMP, MEP, MBzP, MEHP, mono(2-ethyl-5-hydroxyhexyl) phthalate, and mono(2-ethyl-5-oxohexyl) phthalate. There was an association between MEP and DNA damage. MEHP, a metabolite of DEHP, was associated with DNA damage after adjustment for the oxidative DEHP metabolites mono(2-ethyl-5-hydroxyhexyl) phthalate, and mono(2-ethyl-5-oxohexyl) phthalate. There is an indication of altered sperm motility and sperm DNA damage (as measured in chromosomal breaks) after exposure to DEHP and several other phthalates.

Male fertility

A Swedish epidemiologic study by Modigh and colleagues (2002) assessed the association between occupational exposure to DEHP and male fertility as determined by evaluating the time to pregnancy in 227 couples and their 397 pregnancies where male partner was working in a plant producing polyvinyl chloride (PVC) plastics. Exposure assessment was based on air measurements at work place and questionnaire information on work tasks and locations. Time to pregnancy was compared between three exposure categories of no exposure, low (<0.1 mg/m3) and high (>0.1 mg/m3). There was no association between exposure and time to pregnancy.

Testicular cancer

Two epidemiologic studies of testicular cancer have used source based exposure assessment rather than measurements of specific phthalates concentrations (Hardell et al. 1997, Hansen 1999). Hardell and colleagues (1997) conducted a case-control study of the association between occupational exposure to PVC plastics and testicular cancer. They identified 148 testicular cancer cases and 315 controls from the Swedish Cancer Registry. Exposure assessment was based on questionnaire information on occupations with probable PVC exposure. There were 6 exposed cases of seminoma and 2 exposed controls resulting in an adjusted odds ratio of 5.6 (1.1-196). No other association of cancer with plastics exposures was identified. Hansen (1999) conducted a case-controls study of 3745 and 7212 controls using registry-based data on occupational history. There was no association between the risk of testicular cancer and exposure PVC plastics based on job category.

Respiratory health

Øie et al. (1997) hypothesized that di(2-ethylhexyl) phthalate (DEHP) causes airways inflammation by mimicking some prostaglandins and thromboxanes with a similar chemical structure. Some monophthalates have been shown to promote cytokine IL-6 and IL-8 production in the human epithelial cell line A549, indicating a potential role in inflammatory processes (Larsen et al. 2001b).

Jaakkola and colleagues (1999) conducted a matched case-control study of 251 cases of bronchial obstruction and controls from a prospective Oslo Birth Cohort Study. Bronchial obstruction was defined as two or more episodes with symptoms and signs of bronchial obstruction. Trained experts characterized the interior surfaces and exposure assessment was based on the type of materials. The risk of bronchial obstruction was greater in the presence of PVC in the floors (adjusted OR = 1.89, 95 percent CI: 1.14, 3.14). The risk of bronchial obstruction was also related to a plasticizer exposure index (adjusted OR 2.72, 95% CI 1.50-4.91). Further analyses showed that the relation of bronchial obstruction to a plasticizer exposure index was stronger in homes with low air change than in those with high air change (Øie et al. 1999).

In a population-based cross-sectional study of 2568 Finnish children aged 1 to 7 years, the risk of wheezing, persistent phlegm, weekly nasal congestion or excretion, and respiratory infections were related to the presence of plastic wall materials at home (Jaakkola et al. 2000).

Bornehag and colleagues (2004) conducted a case-control study of Swedish children aged 3 to 8 years. The 198 cases included subjects with persistent allergic symptoms (106 with asthma, 79 with rhinitis and 115 with eczema) and 202 controls were free of these symptoms, both recruited from a population-based cohort of 10,852 children. The case status was related to the presence of PVC flooring in the bedroom with an adjusted OR (odds ratio) of 1.59 (95% CI (confidence interval) 1.05-2.41). The dust concentrations (milligram per gram dust) of six phthalates were determined: DEP, DBP, DIBP, BBzP, DEHP, and DINP. Median house dust concentrations of BBzP were higher in the bedrooms of cases than controls. The risk of allergic rhinitis and eczema was related to the house dust BBzP concentrations, whereas the risk of asthma was related to concentration of DEHP (Bornehag et al. 2004). Jaakkola and colleagues (2006) conducted a population-based incident case-control study to assess the relations between different types of interior surface materials and recent renovations at home and at work and the risk of asthma in adults. They recruited systematically all new cases of asthma during a 2.5-year study period (1997-2000) and randomly selected controls from a source population consisting of adults 21 to 63 years of age living in South Finland. The clinically diagnosed cases consisted of 521 adults with new asthma and the controls of 932 adults fulfilling eligibility criteria. In logistic regression analysis adjusting for confounding, the risk of asthma was related to the presence of plastic wall materials (adjusted odds ratio (OR) = 2.43, 95% confidence interval (CI): 1.03, 5.75) and wall-to-wall carpet at work (adjusted OR = 1.73, 95% CI: 0.74, 4.09), the latter in particular in the presence of mold problems (adjusted OR = 4.64, 95% CI: 1.11, 19.4). Use of floor levelling plaster at home during the past 12 months was also a determinant of onset of asthma (adjusted OR = 1.81, 95% CI: 1.06, 3.08).

These studies suggest correlation between PVC and/or phthalate exposure and obstructive respiratory symptoms and asthma.

3.4.15. Conclusion

The key factors influencing to the risks to individual patients arising from the use of DEHP used in medical devices are:

- Background exposure
- Exposure dose (leaching from each medical device used)
- Vulnerability of patients (including the time window of the exposure)

The general population is exposed to DEHP through a variety of routes with food being the primary source. Several metabolite excretion studies suggest a non-negligible exposure to DEHP in the whole general population. In general, DEHP exposure assessments from probabilistic calculations from DEHP measurements in environmental media and dose reconstructions from urinary metabolite levels agree within an order of magnitude. Most recent studies suggest a current median exposure of 2 to 5 µg/kg bw/day, whereas the 95th percentile is estimated to be between 6 and 17 µg/kg bw/day. Children may have somewhat higher body burden of DEHP than adults. There are indications that exposure to DEHP in the general population has decreased during the last few years.

Medical procedures using PVC medical devices can lead to DEHP exposures much higher than the background levels, although such exposure is of limited duration (Tables 6-8). Also during voluntary medical treatments such as apheresis procedure to donate blood products may result in significant exposure to DEHP. The extent of exposure largely depends upon the medical treatments given and the duration of the treatment (Tables 6-8). Premature neonates in intensive care can receive even higher DEHP exposures than adults relative to their body weight (up to 35 mg/kg bw over 10 day period). This exposure may be even higher than the doses observed to induce reproductive toxicity in animals. In effect, this means that there is no margin of exposure (MoE) for certain procedures. However, this is justified by the beneficial effects of these procedures.
Treatment categories involving a potential high exposure are:

- Multiple procedures in pre-term neonates
- Total Parenteral Nutrition (TPN) in neonates
- ECMO in neonates
- Exchange transfusion in neonates
- Haemodialysis patients
- Enteral nutrition in neonates and adults
- Heart transplantation or coronary artery bypass graft surgery
- Massive infusion of blood into trauma patient
- Transfusion in adult undergoing ECMO

The animal and epidemiological studies enable the likely sensitive patient groups to be identified. Animal studies have identified two lead effects liver tumours and changes in the male reproductive system. The NOAEL for the reproductive toxicity is 4.8 mg/kg bw /day. In respect to the liver tumours there is good scientific evidence from mechanistic and other studies to indicate that DEHP is unlikely to cause this effect in man. However, for the effect in the male reproductive system both mechanistic and epidemiological findings indicate a potential hazard for man. Immature young animals are more susceptible to testicular toxicity by DEHP than older mature animals. The EU risk assessment for DEHP (ECB 2006) identified the most critical effects as on the testes, fertility, development (anogenital distance), and kidney (repeated dose). The sensitivity for such endocrine effects is highest during gestation and the first month after birth when the most sensitive organs are developing. It has to be considered that there is the potential exposure for infants to other phthalates (chapter 3.5) that are toxic to reproduction, which may have via similar mechanisms of action as DEHP.

The summary of epidemiological findings on DEHP and/or other phthalates with similar mechanism is as follows:

- Hypospadias and cryptorchism: no evidence for potential endocrine disrupting effects
- Anogenital distance: limited indications based on one study
- Birth weight and gestational age: insufficient evidence based on one study
- Pubertal development of young females: insufficient evidence based on one study, not confirmed in another study
- Phthalate ester levels affect the severity of endometriosis: insufficient evidence
- Male fertility: no association between exposure and time to pregnancy, no effect on fertility in very low birth weight males;
- Semen quality: contradictory reports on the effects of DEHP
- Testicular cancer: no association between this cancer and exposure to PVC plastics
- Respiratory health: phthalate exposure correlates weakly with obstructive respiratory symptoms and asthma

Epidemiological studies on DEHP assessed in this report by themselves do not establish a cause-effect relationship for harmful effects on humans. However, analysing the animal and human data and mechanistics studies as a whole it can be concluded that male foetuses of pregnant women and male neonates can be considered as potential groups at risk in view of the exposure levels above those that induce reproductive toxicity in rodent animal studies. These high exposure levels during certain medical procedures have to be seen in the light of treatment needed and the availability of suitable alternatives for each medical treatment. In addition data available on non-human primate studies do not indicate effects of DEHP on the male reproductive system.

It should be noted that medical devices made from plasticized PVC provide many effective treatments and that DEHP is a particularly effective plasticizer. In addition to its beneficial effect on mechanical properties, DEHP also stabilises the membranes of red blood cells enabling blood product storage in PVC blood bags for several weeks.

3.5. Alternative plasticizers in PVC medical devices

3.5.1. Introduction

The information available for the potential alternative plasticizers for DEHP in PVC medical devices use is presented in Annex I. Both publicly available information (published papers) and information submitted by stakeholders were considered. For each individual alternative a conclusion is presented in the Annex I.

The safety evaluation of medical devices and their composing materials including material characteristics, leaching and toxicology is described in the ISO/CEN 10993 series on

Biological Evaluation of Medical Devices (ISO, Geneva, Switzerland, CEN, Brussels, Belgium).

3.5.2. Exposure to alternative plasticizers

When alternatives are used as replacement for DEHP, it can be expected that for the use in medical devices the contact of patients with these alternatives is similar to DEHP. In terms of quantitative exposure (mg/kg bw) obviously differences may occur depending on the actual amount of plasticizer present in the medical devices used and the leaching properties of these alternatives.

The patient exposure to plasticizers in medical devices depends not only on the substance used, but also on a number of other factors. The time and area of contact between the plastic device and the biological medium/tissue is important, as well as the character of the biological medium. The plasticizer concentration in the polymer may also be important and mechanical stress of tubing in peristaltic pumps and agitation of storage samples may increase the leaching of the additives in the medium. All these variables make it difficult to compare leaching measured in different studies, and comparisons of different plasticizers under identical conditions are therefore the most useful results.

A lot of data on leaching of polymer additives from food packaging materials and some data on plasticizer leaching from PVC toys have been published, and a few standardised test systems have been developed. Food simulants are used to mimic leaching of plasticizers and other additives in different types of food stored under specified temperatures and different time periods, where the concentration of the additive is analysed in the simulant. Artificial saliva and gastric juice simulants have been used to estimate leaching of chemicals from mouthing and ingestion of toys/toy materials.

These data have, however, limited use in quantification of exposure from medical devices. Thus, the leaching rates of plasticizers from food packaging materials may be useful in the quantification of leaching of these substances during storage of biological materials in plasticized PVC container under static conditions. The leaching rates obtained via toy testing may have application in quantification of plasticizers under dynamic conditions, but only in aqueous medium. However, the comparison of leaching rates from medical devices of various plasticizers measured by testing of food packaging packaging and toy testing will indicate the relative leaching of alternative plasticizers compared to that of DEHP. As exposure data on DEHP from PVC medical devices containing this plasticizer is available for most critical procedures, exposure data on alternative plasticizers can be generated/extrapolated on the basis of relative leaching rates using DEHP exposure data (see section 3.4) as benchmark. Standard test methods for measuring the leaching rates of components from medical devices (ISO 10993) are available, and information can be obtained from investigations where leaching of alternative plasticizers is compared under identical conditions. This kind of information for the investigated DEHP alternatives has, however, not been available to the SCENIHR.

In a comparative study of leaching of plasticizers to different feeding solutions (Welle et al. 2005) DINCH, TOTM and ATBC were compared with DEHP. The feeding solutions contained 4.4 - 10% fat, and commercially available feeding sets with 29 - 49% plasticizer were used, except for DINCH, which was in a pilot application tube containing 30% of the plasticizer. The leachings were followed with chemical analyses for 24 hours. The leaching rates of various plasticizers were relatively constant over this period, except for ATBC where the leaching decreased with time. The latter may be explained by the high leaching rate for ATBC, at least ten times higher than for DEHP. The DINCH leaching were three to ten times lower than that for DEHP, while the release of TOTM was extremely low and in one experiment almost two orders of magnitude lower than the leaching of DINCH. In the TOTM

experiment the authors also measured DEHP and found 40 times more of the phthalate than of the trimellitate, which was probably due to DEHP impurity in the TOTM.

For TOTM a comparison (Senshu et al. 2004) between PVC infusion lines containing this compound and DEHP was reported. Significantly higher leaching was found for DEHP (about thirty times higher in one case). In another study (Kambia et al. 2001) PVC tubes for haemodialysis plasticized with DEHP and TOTM were compared. The leaching of DEHP was about three times higher than that of TOTM, but the latter also emitted DEHP. The leaching of DEHP from TOTM containing products is associated with the content of DEHP impurity in TOTM.

In a recently published study, 5 cm of PVC nasogastric tubes containing DEHP or polyadipate were incubated with feeding solution and gastric juice (Subotic et al. 2007). Although at least 10 times lower leaching was observed compared to that of DEHP, no conclusion can be made from this study because the contents of the two plasticizers in the tubings are not described.

PVC was blended with different plasticizers and moulded thin sheets of these materials in order to compare several properties. The plasticizers included were DEHP, DEHA, ATBC and BTHC. A few of the results are presented in Table 10. The higher extraction into the oil reflects the lipophilic character of these esters. The biggest difference between the compounds was seen in the soapy water, being approximately of a factor of five between the extremes.

Table 10. Extraction of some plasticizers from PVC (48 hours at 25°C)

	Extracted fraction (%) of			
Solvent	**DEHP**	**DEHA**	**ATBC**	**BTHC**
Water	0.7	1.5	1.2	1.7
Soapy water	2.7	11.0	9.5	2.2
ASTM Oil #3	11.4	34.7	10.9	15.7

In a comparison between leaching of BTHC and DEHP into blood in PVC bags containing these substances (Kandler 1998), a slightly lower leaching of BTHC could be found.

The leaching of COMGHA to some simulants have been tested (Kristoffersen 2005) and compared with the corresponding data for DEHP and DINP (see Table 11). The leachings to aqueous media seem to be much smaller for the COMGHA than for the phthalates tested, while in lipophilic media/substances the leaching was of the same order of magnitude. Different data were, however, available to EFSA in their evaluation (EFSA 2004) and are also included in Table 11. This highlights the difficulties to compare results from leaching studies.

Table 11. Leaching from PVC containing COMGHA (40%), DEHP (40%) and DINP (42%), respectively

Plasticizer	Reference	Leaching mg/ dm^2		
		3% acetic acid	**15% ethanol**	**Sunflower oil**
COMGHA	Kristoffersen 2005	0.0058	0.0055	368
DEHP	Kristoffersen 2005	2.83	1.31	466
DINP	Kristoffersen 2005	-	-	420
COMGHA	EFSA, 2004	0.06	0.06	10.3

It is not possible to draw any far reaching conclusions regarding the relative leachings of the investigated plasticizers based on the studies referred to above. A couple of them identify the leachings of TOTM to be several orders of magnitude lower than that of DEHP, and ATBC leaching were found to be higher than that of DEHP in a couple of investigations. The general impression is, however, that the leachings of the remaining plasticizers are rather similar, which is not too surprising given their similar structures and properties. For some plasticizers 5 to 10 fold lower leaching rates were observed.

3.5.3. Toxicity of the alternative plasticizers

In general the toxicity of the alternative plasticizers is less well described than for DEHP, although for some plasticizers ECB risk assessment reports are available. Information on each of the alternatives considered is presented in Annex 1.

3.5.4. Conclusions on the risks of the alternative plasticizers

To compare the toxicity a short summary of the potential genotoxicity, the carcinogenicity, repeated dose toxicity and reproductive toxicity are summarised in Table 12. In the tables NOAEL is shown as the lowest effects in male or female rat.

The information of the leaching from alternative plasticizers is sparse but may be expected to be of same order of magnitude. The margin of exposure for DEHP in neonate seems to be very low. For blood transfusion peak values up to 22 mg/kg bw/day have been estimated showing a dose 4 times higher than NOAEL for DEHP.

Table 12. NOAEL of DEHP compared with some alternative plasticizers.
The critical endpoint is shown to indicate that for some of the chemicals it is different from reproductive effects.

Plasticizer	NOAEL mg/kg bw	Reproductive Toxicity	Critical endpoint	Exposure Range (neonates) µg/kg bw/day
DEHP	4.8	Yes	Reproduction	42-2300
ATBC	100	No	Decreased bw	
COMGHA	5000	No data	Decreased bw	
BTHC	250	No	Liver weight	
DEHA	200	Yes	Foetotoxicity	
DINCH	107	No	Kidney*	
DINP	15 (88)	No/Yes	Liver	
DOTP	500-700	No	Developmental	
TOTM	100	Yes	Reproduction	

bw: body weight
* Kidney effects in male rats due to alpha-2-u macroglobulin, a mechanism not relevant to man

Considering similar leaching rates, the margin of safety of other plasticizers will be least 20 times higher for most alternatives. Thus differences in leaching rates even at one order of magnitude higher than DEHP may be acceptable.

The toxicity of alternative plasticizers is shown for cancer and mutagenicity effects in Table 13.

Table 13. The cancer and mutagenicity effects and maternal toxicity of plasticizers

Plasticizer	Repeated dose Toxicity, NOAEL	Genotoxicity	Carcinogenicity	Maternal toxicity mg/kg bw/day

	mg/kg bw/day			
DEHP	29 (male rat)	Negative	LOAEL 320 (male rat)	LOAEL 750 (rat)
COMGHA	5000	Negative	No data	No data
ATBC	100	Negative	Negative	NOAEL 100 (rat)
BTHC	250	Negative	Negative	NOAEL
DEHA	200	Negative	NOAEL 1250	NOAEL 400 (rat)
DINCH	107	Negative	Negative	NOAEL 1000 (rat)
DINP	15 (88)	Negative	Kidney	LOAEL 750 (rat)
DOTP	500-700	Negative	Negative	NOAEL 458 (rat)
TOTM	100	Negative	No Data	NOAEL

It can be concluded that DEHP is causing the most severe reproductive effects in animal studies evaluating toxicity. DEHA, DINP, and TOTM are also causing reproductive toxicity, but in doses more than 20 times higher. COMGHA and TOTM could not be evaluated for all endpoint due to lack of data. Regarding the alternatives, for some compounds sufficient toxicological data is available to indicate a lower hazard compared to DEHP.

However, a risk assessment of these alternative plasticizers could not be performed due to a lack of human exposure data. For others, information on the toxicological profile is inadequate to identify the hazard. This limits the proper evaluation of the potential to replace DEHP by alternative plasticizers. The risk and benefit should be carefully evaluated for each individual medical device and each medical procedure in which the alternative needs to be used.

3.6. Combined exposure to plasticizers

Combined exposure of different population and subpopulation is possible and may occur at different times or together. Due to the wide use of DEHP in the society humans may be exposed from many different sources and exposed to other phthalates as well. It is obvious that combined exposure to DEHP, DBP, BBP, DIBP, and DINP having the same mechanism of action may potentially cause at least an additive effect. Combined exposure to DEHP and DINP had showed an additive effect (Borch et al. 2004). In general a common mechanism might exist if two compounds:

- Cause the same critical effect
- Act on the same molecular target at the same target tissue, and
- Act by the same toxicological mechanism of action and may share a common toxic intermediate.

This will probably be the case for combined exposure to the five mentioned phthalates. The potency of the different phthalates should be considered. DEHP and DBP are almost equal in potency. DIBP and BBP are less potent and DINP seems to have the smallest effect considering their effect on steoridogenesis in foetal male rats.

The chemical structures of some alternative plasticizers show that some of them have a possibility to form the same metabolite 2-ethylhexanol; this is the case for DEHA, DOTP, TOTM and DEHP.

3.7. Potential alternative polymer plasticizers in PVC medical devices

In addition to the potential alternative plasticizers discussed above, another alternative to phthalates is represented by the use of "polymeric plasticizers", that is, by high molecular weight solid polymers soluble in PVC in large proportions. These polymers, when blended with PVC by conventional processing, give polymeric alloys, that is, homogeneous blends constituted by a single thermodynamically stable phase. Their macromolecular dimensions lead to segment-segment entanglements with PVC matrix, thus strengthening interactions, reducing diffusion, and hindering leaching outside the blend. Polymeric plasticizers of PVC are typically aliphatic polyesters. Many of these are structurally related with polyesters commonly employed as components of drug delivery systems, and are biodegradable and biocompatible. Their low solubility in water further prevents extraction by aqueous media.

Extensive literature reports on polyester/PVC blends show (Lindström and Hakkarainen 2006, Hakkarainen 2005) that a number of homopolymeric and co-polymeric structures are in principle eligible as constituents of soft PVC formulations, and that even different class of polymers, as for instance polypropylene glycols, might be used to this purpose. However, a number of basic requirements must be fulfilled in order to fully exploit polyesters for their potential as PVC plasticizers. Besides being miscible in all proportions with PVC, their glass transition temperature must be lower than 0°C and, in addition, they must show no tendency to crystallise with time within the alloy. In fact, after crystallisation, they separate into crystalline domains, which impart opacity and decrease plasticizing effect. In order to minimize migration their molecular weight must be medium-high. However, in practice polymers with average molecular weight as low as 1000 g/mol is used. Polymeric plasticizers generally make the compounds more difficult to process (Shah and Sherdukte 2003, Lindström and Hakkarainen 2007). Most of these compounds are experimental (Ferruti et al. 2003) and insufficent information is available to assess the use and safety of these compounds in medical devices.

3.8. Conclusion

The general population is exposed to DEHP through a variety of routes with food being the primary source. Median exposure is estimated to be 2 to 5 µg/kg bw/day. Children may have somewhat higher body burden of DEHP than adults.

Medical procedures using PVC medical devices can lead to DEHP exposures much higher than the background levels. However, the extent of exposure largely depends upon the medical treatments given and the duration of the treatment. In adults, highest doses of DEHP may result by transfusions of blood components reaching up to several mg/kg bw/day. It has been shown that also voluntary medical treatments such as apheresis procedure to donate blood products can cause significant exposure to DEHP. Premature neonates in intensive care can receive even higher DEHP exposures than adults relative to their body weight.

This is of concern in view of rodent animal studies showing that immature young animals are more susceptible to testicular toxicity by DEHP than older mature animals. Neonates may therefore be considered to be potentially at risk for the adverse reproductive and developmental effects of DEHP. As for adults the extent of exposure varies depending on medical procedures conducted, and in some cases exposure in the mg/kg bw/day range may easily be reached. For blood transfusion procedures peak values up to 22 mg/kg bw/day have been estimated. A limited number of follow-up studies of highly exposed neonates and workers did not indicate an effect of DEHP on the human male reproductive system. In addition data available of non human primate studies do not indicate effects of DEHP on the male reproductive system.

Epidemiological studies on DEHP assessed in this report do not establish a cause-effect relationship for harmful effects on humans. However, even in the absence of clinical or epidemiological evidence for harmful effects in humans, some concern may be raised in view of the exposure levels above those that induce reproductive toxicity in rodent animal studies. The exposure levels during certain medical procedures have to be seen in the light of treatment needed and the availability of suitable alternatives for each medical treatment.

It is also noted that DEHP has beneficial properties in stabilising the membranes of red blood cells enabling blood storage for several weeks

Regarding the alternatives, for some compounds sufficient toxicological data is available to indicate a lower hazard compared to DEHP. However, a risk assessment of these alternative plasticizers could not be performed due to a lack of human exposure data. For others, information on the toxicological profile is inadequate to identify the hazard. This limits the proper evaluation of the potential to replace DEHP by alternative plasticizers. The risk and benefit should be carefully evaluated for each individual medical device and each medical procedure in which the alternative needs to be used.

4. OPINION

In view of the complexity of the questions addressed in the Terms of Reference. the Committee decided to concentrate on the risk assessment of plasticizers used in PVC in this opinion. Whilst recognising that there are several non-PVC based materials that could provide effective materials for use in medical devices, this opinion does not address these materials. Although the published Call for Information included both alternative plasticizers and alternative materials, only the former was submitted. The Committee recognized that there may be need for evaluation of these alternative non-PVC materials in the future.

There have been concerns over possible health effect of DEHP for many years. Several times CSTE, CSTEE and SCMPMD have expressed their opinions on different aspects of the reproductive toxicity of phthalates and more specifically on DEHP. Since the last opinion on medical devices from September 2002 expressed by SCMPMD new information on the exposure and possible reproductive effects of DEHP has appeared in the literature. A better understanding of the mechanism of the antiandrogenic effects in animal models has evolved after 2002.

Recent information on the exposure of the general population and especially of the vulnerable groups raised a concern on the potential toxicity of DEHP. Vulnerable groups are male infants, male offspring of pregnant and breastfeeding women undergoing certain medical procedures that may result in general in short-term exposure to relatively high levels of DEHP.

The exposure of the general population to DEHP is already significant. The main source of DEHP for the general population is dietary, followed by inhalation of air. The exposure in adults ranges from a few µg up to 25-30 µg /kg bw/d. There are important differences among populations and individuals associated with various dietary habits and lifestyle. Infants and children are exposed to higher levels than adults, on a body weight basis.

Certain medical procedures involving plasticized PVC are already known to cause considerable exposure to phthalates. These procedures include:

- Multiple procedures in pre-term neonates
- Total Parenteral Nutrition (TPN) in neonates
- ECMO in neonates
- Exchange transfusion in neonates
- Enteral nutrition in neonates and adults
- Haemodialysis
- Heart transplantation or coronary artery bypass graft surgery
- Massive infusion of blood into trauma patients
- Transfusion in adults undergoing ECMO

However, for many of these procedures the actual extent of exposure is still unknown or spans several orders of magnitude. Research is needed to determine (i) the multiple sources and pathways of human exposure to phthalates; (ii) whether exposure to phthalates at the levels found in the general population is a cause for health concern; and (iii) to what extent human exposure to phthalates may impair human health.

Data available on the exposure to DEHP show that DEHP exposure levels of neonates during certain medical procedures are in the same order of magnitude or even higher than doses inducing reproductive toxicity in animal studies. This is of concern in view of animal studies showing that immature young animals are more susceptible to testicular toxicity by DEHP than older mature animals. Neonates may therefore be considered to be at risk for the adverse reproductive and developmental effects of DEHP. In addition, they may be exposed to other phthalates especially DBP and DIBP, and these phthalates may act additively with DEHP.

There is limited evidence indicating a relation between DEHP exposures and some adverse effects in humans. However, the few follow-up studies after high DEHP exposures in neonates and in occupational settings, performed sofar, did not indicate that there is an effect of DEHP on fertility and/or the human male reproductive system. Regarding the effect of DEHP on semen quality and female development contradictory results were reported. It is recognised that especially the potentially high exposure during medical treatments may raise concern, even in the absence of clinical or epidemiological evidence for harmful effects in humans. Nevertheless, irrespective of the potential risk, one has to realise that especially in neonatal intensive care units, these neonates depend for their survival on a multitude of medicines and medical procedures including the use of medical devices.

Sofar, there is no conclusive scientific evidence that DEHP exposure via medical treatments has harmful effects in humans. However, further studies are required to confirm or reject the suggestions of adverse effects of DEHP in humans.

Some alternatives may be suitable to replace DEHP in certain medical devices, while for other devices it may be difficult to obtain the same functionalities as PVC plasticized with DEHP. A risk assessment for the alternatives could not be performed due to a lack of exposure data. For other possible alternatives, adequate toxicity data is also lacking. The risk and benefit of using alternative plasticizers should be evaluated case by case. In addition, it is known that DEHP containing PVC can contribute to the stability of blood cells. However, this has not been evaluated for most alternative plasticizers.

Responses to the questions in the Terms of Reference

Question 1.

Update of the scientific opinion adopted in September 2002 on DEHP plasticized medical devices. Taking into consideration recent scientific developments, the SCENIHR is requested to review and update, if appropriate, the scientific opinion adopted in September 2002 on "Medical Devices containing DEHP Plasticized PVC; neonates and other groups possibly at risk from DEHP toxicity".

In particular, the Scientific Committee is requested to evaluate:

- *If DEHP in PVC plasticized medical devices is a cause for concern to neonates and children in paediatric care, in particular in relation to male fertility and tissue development,*
- *If there are other patient groups at risk, in particular in view of clinical procedures resulting in high exposure,*
- *If it is possible to establish Tolerable Intake Values of DEHP leaching from soft PVC as a basis for risk assessment for high risk patient groups, taking into account the route of exposure.*

Compared to the previous opinion of the SCMPMD, the new information indicates that there is still a reason for some concern for prematurely born male neonates. This concern is instigated by the potential high human exposure especially during certain medical procedures which may be transiently above the dose inducing reproductive toxicity in animal studies, and limited epidemiological evidence suggesting an adverse effect on the male reproductive system. However, the few follow-up studies after high DEHP exposures in neonates performed sofar, did not indicate that there is an effect of DEHP on the development of the human male reproductive system.

Sofar, there is no conclusive scientific evidence that DEHP exposure via medical treatments has harmful effects in humans. However, further studies are required to confirm or reject the suggestions of adverse effects of DEHP in humans.

Other patient groups with relatively high DEHP exposures, which may result in some risk, are those requiring repeated medical procedures, including male foetuses of pregnant women.

Recently a Tolerable Daily Intake (TDI) value of DEHP has been established and published in the EU Risk Assessment Report (RAR 2006). The TDI for DEHP is 48 µg per kg body weight per day, which was based on a No Observed Adverse Effect Level for reproductive effects in rats. In view of the potential high exposure to DEHP during certain medical procedures and a very special group of patients involved, the use of TDI is not considered appropriate in these procedures.

Question 2.

Medical devices containing alternative plasticizers: possible risk for certain uses or to certain patient groups. Since alternative DEHP free medical devices have been developed and are used to treat patients, the Scientific Committee is requested to evaluate the potential risks of currently available alternatives in relation to patient health, when used in medical devices.

The non-PVC alternative materials were not evaluated.

There are alternative plasticizers to PVC and also non-PVC alternative materials available. For the alternative plasticizers a generic exposure assessment could not be performed due to a lack of relevant use and human exposure data. For other possible alternatives, information on the toxicological profile was lacking. The risk and benefit should be carefully evaluated according to established protocols, for each individual medical device and each medical procedure in which the alternatives are intended to be used. For some alternative plasticizers, sufficient toxicological data is available to indicate a lower hazard compared to DEHP. The functionality of these plasticizers should be assessed before they can be used as an alternative for DEHP in PVC medical devices.

5. COMMENTS RECEIVED FROM THE PUBLIC CONSULTATION

The public consultation of the preliminary opinion took place from 15 October to 26 November 2007 and information about it was communicated to various stakeholders. During the consultation 21 contributions were received, 13 of which came from industry or industry associations, 4 from individuals, 3 from public authorities and 1 from an NGO.

In evaluating the responses from the consultation, submitted material has only been considered for revision of the opinion if

1. it is directly referring to the content of the report and relating to the issues that the report addresses,

2. it contains specific comments and suggestions on the scientific basis of the opinion,

3. it refers to peer-reviewed literature published in English, the working language of the SCENIHR and the working group,

4. it has the potential to add to the preliminary opinion of SCENIHR.

Each submission which meets these criteria has been carefully considered by the Working Group. Overall, many of the comments were of good quality and the opinion has been partly revised based on these comments. The literature has been updated with relevant publications up to early 2008.

The evaluation of the existing and additional literature on epidemiological studies on harmful effects of DEHP in man showed that there was no conclusive scientific evidence for a harmful effect of DEHP in humans. However, it is recognised that especially the potentially high exposure during medical treatments may raise a concern, even in the absence of clinical or epidemiological evidence, for harmful effects in humans. It is recommended that further studies are performed to confirm or reject the suggestions of adverse effects of DEHP in humans.

There is some concern for harmful effects of DEHP on humans. Prematurely born male infants are considered to be a high risk group as for this group the DEHP exposure may be transiently above the dose inducing reproductive toxicity in animal studies.

6. MINORITY OPINION

None.

7. LIST OF ABBREVIATIONS

2cx-MMHP	Mono-[2-(carboxymethyl)hexyl] phthalate
2-EH	2-Ethylhexanol
5OH-MEHP	Mono-(2-ethyl-5-hydroxyhexyl) phthalate
5cx-MEPP	Mono-(2-ethyl-5-carboxypentyl) phthalate
5oxo-MEHP	Mono-(2-ethyl-5-oxohexyl) phthalate
AGD	Anogenital distance
AGI	Anogenital distance (mm/kg bw)
COMGHA	Glycerides, Castor-oil-mono-, hydrogenated, acetates
ASTM	American Society for Testing and Materials
ATBC	Acetyl-tri-n-butyl citrate
AUC	Area under curve
BBP	Butyl benzyl phthalate
BTHC	Buturyl-tri-n-hexyl citrate
CAPD	Continuous ambulatory peritoneal dialysis
CI	Confidence interval
CAS	Chemical Abstracts Service
CERHR	Center for the Evaluation of Risks to Human Reproduction
CPs	Chlorinated paraffins
cx-MINP	Carboxylated MINP
DBP	Di-n-butyl phthalate
DEHA	Di(2-ethylhexyl) adipate
DEHP	Di(2-ethylhexyl) phthalate
DEP	Diethyl phthalate
DG	Directorate General
DIBP	Di-iso-butyl phthalate
DIDP	Di-iso-decyl phthalate
DINCH	Di-iso-nonyl 1,2-cyclohexanedicarboxylate
DINP	Di-iso-nonyl phthalate
DMP	Dimethyl phthalate
DOP	Di-n-octyl phthalate
DOTM	Dioctyl trimellitate
DOTP	Dioctyl terephthalate
E2	Estradiol
ECB	European Chemical Bureau
ECDC	European Centre for Disease prevention and Control
ECHA	European Chemicals Agency

ECMO	Extracorporeal membrane oxygenation
EFSA	European Food Safety Authority
ELO	Epoxidised linseed oil
EMEA	European Medicines Evaluation Agency
ESBO	Epoxidised soya bean oil
FSH	Follicle-stimulating hormone
FDA	US Food and Drug Administration
fT	Free testosterone
GLP	Good laboratory practice
IARC	International Agency for Research on Cancer
JEM	Job-exposure matrix
PVC	Epoxidised linseed oil
LH	Luteunizing hormone
LOAEL	Lowest observed adverse effect level
MBP	Mono-n-butyl phthalate
MBzP	Monobenzyl phthalate
MBBP	Monobutylbenzylphthalate
MEHP	Mono(-2-ethylhexyl) phthalate
MEP	Monoethyl phthalate
MIBP	Mono-iso-butyl phthalate
MINP	Mono-iso-nonyl phthalate
MMP	Monomethyl phthalate
MOTM	Monooctyl trimellitate
MOTP	Monooctyl terephthalate
NOAEL	No observed adverse effect level
NOEL	No observed effect level
NICU	Neonate intensive care unit
NTP	US National Toxicology Programme
OH-MINP	Hydroxylated MINP
OR	Odds ratio
oxo-MINP	Oxygenated MINP
PPARα	Peroxisome-proliferator activated receptor
PVC	Polyvinylchloride
RAR	Risk Assesment Report
SANCO	Directorate General for Health and Consumer Protection
SAP	Stearic acid, 2,3-bis(acetoxy)propyl ester
SCCP	Scientific Committee on Consumer Products

SCHER	Scientific Committee on Health and Environmental Risks
SCENIHR	Scientific Committee on Emerging and Newly-Identified Health Risks
SCMPMD	Scientific Committee on Medical Products and Medical Devices Opinion
SHBG	sex-hormone binding globulin
SF-1	steroidogenic factor-1
TDI	Tolerable Daily Intake
Tg	Glass transition temperature
Tm	Melting Temperature
TOTM	Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate
TPA	Terephthalic acid
TPN	Total parental nutrition
TOTM	Trioctyl trimellitates

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ANNEX I evaluation of individual plasticizers

No information was submitted on the DINP and DEHA plasticizers, but they have been included in this assessment as they are already being used to substitute DEHP in a number of applications.

1. ATBC (Acetyl tri-n-butyl citrate)

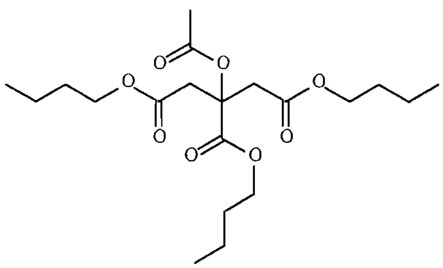
1.1. Physico-chemical properties

CAS Reg. No.:77-90-7

Synonyms: Citroflex A-4; 2-(acetyloxy)-1,2,3-propanetricarboxylic acid, tributyl ester; 1,2,3-propanetricarboxylic acid, 2(acetyloxy)-, tributyl ester; acetylcitric acid, tributyl ester; citric acid, tributyl ester, acetate; tributyl acetylcitrate; tributyl O-acetylcitrate; tributyl-2-(acetyloxy)-1,2,3-propanetricarboxylate; tributyl citrate Acetate.

Emperical formula: $C_{20}H_{34}O_8$

Structure:



Molecular weight:	402.5
Melting point:	-80°C
Boiling point:	173°C (1 mm Hg)
	200°C (4 mm Hg)
	326°C (160 mm Hg)
Vapour pressure:	0.052 mm Hg (20°C)
Solubility in water:	20 mg/L
Log Kow:	4.3 (estimated)
Purity:	>99%
Impurities:	Water, volatiles.

1.2. Use

ATBC is used as a plasticizer in cosmetics, in concentration of 0.7 to 7%. The substance is also used as a plasticizer in PVC, adhesives and coatings. For medical devices Johnson (2002) says that the major compound being used is acetyltrihexyl citrate. ATBC has been approved for many food applications, including the use as a flavouring substance, in the USA. The use of ATBC in medical devices is mainly in blood bags, but also about 350 tons are used for the production of medical tubing (Reilly Chemicals, 2006). According to latest information ATBC is mainly used in medical tubings,

1.3. Exposure

No information has been found describing human exposure. Higher leaching rate was found for ATBC as compared to DEHP (Welle et al. 2005).

1.4. Metabolism

ATBC is well absorbed after oral administration with peak blood levels being found between 2 and 4 hours. It undergoes rapid and extensive metabolism to 10 or more polar metabolites. The principal mode of metabolism is hydrolysis of the ester bonds. Blood clearance of C14 labelled ATBC has been shown to be biphasic with corresponding half lives of 3.9hours and 39 hours.

The slow second phase may be an artefact due to some of the radiolabel entering intermediary metabolism pathways. The main route of clearance is through the urine with monobutyl citrate being the principle metabolite found. However some metabolites are also found in the faeces. Whether this indicates that some ATBC is biliary excreted or not absorbed is uncertain. ATBC is also extensively metabolised in human serum and by rat liver samples. The kinetic data indicate that ATBC is very unlikely to accumulate in body tissues even if frequent exposure occurs.

1.5. Toxicity

Acute toxicity

After a single oral dose of 10-30grams per kg kg bw/ per day, administered by gavage, no systemic toxicity has been observed. ATBC can therefore be regarded as virtually nontoxic by the oral route when its administration is acute. In view of its prompt metabolism and excretion and the likelihood that it is metabolised at multiple sites to more polar metabolites it appears unlikely that ATBC will cause significant toxicity at other sites of exposure.

Irritation and sensitisation

ATBC applied dermally to rats produces moderate irritation but has been shown to be a non-irritant following topical application to rabbits. ATBC is not a sensitiser in the guinea pig maximisation test. This finding is supported by the results of studies in which ATBC was applied to the skin of human volunteers

Repeat dose toxicity

Three relevant studies can be identified. The first was a four week range finding study in rats. At the highest dose (equivalent to about 2700 mg/kg bw/day) there was a small decrease in both body and organ weight. However no effects were observed in a second group of rats exposed to the lower dose of around 1000 mg/kg bw/day.

The second study was a 90 day gavage study in male and female rats. Some haematological and biochemical changes in the blood were observed at 300 mg/kg kg bw/day and at 1000 mg/kg kg bw/day there was an increase in liver weight. However no histopathological changes were seen in either test group. At 100 mg/kg bw/day no changes of any kind were seen and therefore this dose may be regarded as the NOEL

A third study involving the in utero exposure of rats is discussed below (in the section on reproductive effects).

Mutagenicity and genotoxicity

A range of in vitro genotoxicity tests have been conducted. In bacterial tests ATBC gave consistently negative results both with and without the presence of a metabolising system. ATBC also gave negative results in two chromosomal aberration studies with rat lymphocytes both in the presence and absence of a metabolising system. However in mouse lymphoma cells a dose dependent increase in mutations at the HK locus was identified in two separate experiments.

An in vivo test has also been conducted using unscheduled DNA synthesis as the endpoint. In rats treated by gavage at either 800 mg or 2000 mg /kg bw/day no increase in UDS could be observed. This finding indicates a low or zero potential of ATBC to cause genotoxic effects in vivo. This conclusion is supported by consideration of the structure of both ATBC and its metabolites for which there are no structural alerts.

Carcinogenicity

A two year oral feeding study has been carried out in rats in which no significant toxic effects relating to ATBC were identified. However this study was not to modern standards and therefore caution should be used in accepting this conclusion. The study does however show that ATBC is not a potent carcinogen and this is in line with the other findings discussed above.

Reproductive studies.

Two relevant studies are available. In the first, a two generation study in rats, ATBC was administered in the diet at levels equivalent to 0, 100, 300 and 1000 mg/kg bw/day. The 300mg and 1000 mg doses produced a decrease in kg bw/ in F1 male rats. In the female rats a decrease in kg bw/ was only observed at the top dose (1000 mg/kg w/day). Thus the NOEL was identified as 100 mg//kg bw/day.

In a second study rats were exposed to ATBC in the diet at doses of 0, 100, 300 and 1000 mg/kg bw/day for four weeks before mating and then throughout the mating period. The offspring (i.e. the F1 generation) were then exposed to ATBC in utero, at birth and for the following 13 weeks. No effects of ATBC could be identified in any of a number of reproductive endpoints. Litter size, survival and growth rates were comparable in the control animals and all the test groups. No adverse effects were identified in any of the offspring examined and no adverse endocrine effects could be detected.

In line with the rat studies summarized above, there were some subtle liver changes (increase in weight, hypertrophy and mild peroxisome proliferation) and renal changes (some changes in urinary composition) in both sexes at the top (1000 mg/kg bw/day) dose. Minor changes were also observed in male animals at the 300 mg/kg bw/ day. A NOEL of 100 mg /kg bw/day can therefore be accepted.

1.6. Human data

No information available on toxicity in humans.

1.7. Conclusion

ATBC is well absorbed following its oral administration. It is rapidly metabolised and excreted from the body. It is unlikely to accumulate in the body following frequent exposure. It has a low toxicity following acute oral administration. In repeat dose studies only non specific effects were found. The oral NOEL was 100mg/kg kg bw//day.
ATBC was found to be non genotoxic and was a very mild hepatic peroxisome proliferator in rats. Moreover in a lifetime bioassay study in rats no dose related tumours were found.

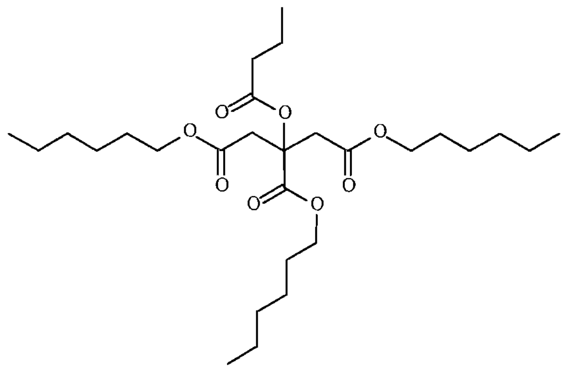
References:

Submission from Reilly Chemicals.

2. BTHC (n-Butyryl-tri-n-hexyl citrate)

2.1. Physico-chemical properties

CAS Reg. No.:	82469-79-2
Synonyms:	Citroflex B-6
Emperical Formula:	$C_{28}H_{50}O_8$
Structure:	



Molecular weight:	514.7
Melting point:	-55°C (pour point)
Boiling point:	
Vapour pressure:	
Solubility in water:	< 1g/L at 25°C
Log Kow:	8.2 (estimated)
Purity:	>99%
Impurities:	Volatiles 1.3%, water max 0.15%, heavy metals max. 10 ppm

2.2. Use

The use pattern for BTHC is similar to that of ATBC. According to latest information BTHC is mainly used in the production of blood bags.

2.3. Exposure

No information has been found describing human exposure. Slightly lower leaching rate was found as compared to DEHP.

2.4. Metabolism

BTHC is well absorbed after oral administration. It is rapidly metabolised by hydrolysis of the ester bonds to a number of metabolites. The principal metabolite is n-hexanol. There are no structural alerts for any of the metabolites. Radiolabelled BTHC is cleared rapidly from the body following iv administration through a combination of urinary and biliary excretion and expired air. BTHC related material does not accumulate in any of the body tissues. The clearance is biphasic with half lives of <15 minutes and >24hours. The latter half life indicates that the radiolabel is widely incorporated into intermediary metabolism pathways. The findings indicate that BTHC is unlikely to accumulate in the body even after a prolonged period of exposure.

2.5. Toxicity

Acute toxicity

No mortality was observed by the oral route in rats for BTHC up to 5000 mg/kg kg bw. Acute iv injection studies with doses of up to 462 mg/kg kg bw/ did not produce any significant adverse effects. In dogs at the same iv dose level the only changes of note observed were in serum glutamate pyruvate transaminase and alkaline phosphatase. It can be concluded that BTHC has a low acute toxicity.

Irritation and sensitisation
One acute study in rabbits indicates that BTHC is a very mild irritant to the skin. In a second study in rabbits Undiluted BTHC (0.1ml) produced a mild and transient reaction when instilled into the eye.

Findings from the maximisation test method in guinea pigs using undiluted BTHC show a slight patchy erythema in one male and one female animal only. A further study using the Buehler method did not show any indication of sensitisation. It can be concluded that under the conditions of these experiments BTHC has a low irritation and sensitisation potential

Repeated dose toxicity
The toxicological properties of BTHC have been investigated by both the oral and iv routes of administration. In an oral dosing study rats were given BTHC by gavage at 0, 250, 500 or 1000 mg/kg kg bw/day for 28 days. No clinical signs of toxicity were observed during the study. Statistically significant increases in the relative liver weight of males were noted at 500 and 1000mg/kg kg bw/ per day but no absolute changes in liver weight were found. Statistically significant changes in urinary pH, aspartate aminotransferase, blood albumin, creatinine and blood calcium were found at the higher dose levels. These findings did not show a clear dose dependency nor were the changes consistent between the sexes. It is difficult to identify a precise NOEL from these findings but a value of 250mg/kg kg bw/ per day is reasonable.

In one study BTHC was administered intravenously to adult rats at dose levels of 5, 50, and 500 mg/kg bw/day for 28 days. At 500 mg/kg bw/day no changes were observed in kg body weight, but there were moderate increases in both liver and spleen weight. These changes were associated with an accumulation of pigment laden macrophages in both organs. This dose group also showed statistically significant changes in some blood parameters. Namely, a decrease in haemoglobin, MCV and platelet levels and an increase in fibrinogen and reticulocyte levels. No other adverse histopathological changes were observed in any organs. No adverse effects were observed at the two lower dose groups.Thus an NOEL by the iv route of 50mg/kg bw//day can be identified.

A study was conducted in neonatal rats. BTHC was administered daily either iv or ip to male and female neonatal rats at 5, 50, and 500 mg/kg kg bw/ per day for eighteen days. At the top dose of BTHC following ip administration an increase in liver weight was noted but without evidence of adverse histopathological changes. After iv administration some histopathological changes were also observed in the lungs (macro granulomas and foreign body infiltration) at each dose.These effects following iv administration are probably due to the route of administration rather than to BTHC itself. By either administration route some tissue damage was noted around the injection sites. The study supports a NOEL by the iv and ip routes of 50mg/kg bw/day.

A specific study was also conducted to investigate the potential of BTHC to cause peroxisome proliferation. Rats were given 3% BTHC in the diet for six weeks. No increase in hepatic peroxisome proliferation was found.

Mutagenicity and genotoxicity
No mutagenic effects were observed for BTHC in several bacterial tests either with or without the presence of a metabolic activation system. In one study the urine, from mice given oral doses of BTHC of up to 1000 mg/kg bw/day, was assessed in various Ames strains of salmonella. No mutagenic effects were observed.

In mouse lymphoma cells BTHC produced different findings in two experiments. In the first there was a slight but statistically significant increase in mutations whereas in a second comparable experiment no significant changes were observed.
Using human peripheral lymphocytes no significant alteration in the incidence of either chromosomal breaks or mitotic frequency was found.

One in vivo study was also carried out in a bone marrow cytogenetic assay. Mice were given an oral dose of 1000 mg/kg bw/day either as an acute dose or daily for five days. In neither study was there any indication of BTHC genotoxicity.

It can be concluded that BTHC is not genotoxic. This conclusion is supported by the lack of structural alerts for both BTHC and its metabolites

Carcinogenicity
A lifetime bioassay test has not been conducted. However it is noted that BTHC is neither genotoxic nor is it a peroxisome proliferating agent.

Reproductive studies.
A fertility study was carried out in albino rats at dietary levels of 0,0.6 0r 1.2% BTHC. Males were exposed to BTHC continuously to BTHC for ten weeks prior to mating and during the mating period. Females were exposed for two weeks before mating, during mating, gestation and lactation. No effects on fertility and other reproductive indices, or on litter weights and pup weights were observed. The kg bw/ of the lactating females exposed to the top dose was slightly lower. No increase in abnormalities in the F1 pups was found.

Developmental toxicity was also examined in rats following the iv administration of BTHC (0, 5, 50, 500 mg/kg kg bw/ /day) on days 6-15 of gestation. No deaths or dose dependent changes in kg bw/ or uterine weight were identified. Nor were any dose related changes observed in resorptions, or embryo or foetal development or foetal toxicity. However in line with the findings from repeat dose studies changes were observed in liver, lung and spleen weight in the mothers.
An NOEL for foetal/embryo toxicity of 500 mg/kg kg bw/day can be estimated in this study.

2.6. Human data

No information available on toxicity in humans.

2.7. Conclusion

BTHC well absorbed following its oral administration. It is rapidly metabolised and excreted from the body. It is unlikely to accumulate in the body following frequent exposure. It has a low toxicity following acute administration by either the oral or iv routes. In repeat dose studies only non specific effects were found. The po NOEL was 250 mg/kg kg bw/day and the iv NOEL was 50 mg/kg kg bw/day.

BTHC was found to be non genotoxic and did not initiate hepatic peroxisome proliferation in rats. No effects of BHTC could be found in rats on reproductive efficiency nor were dose dependent foetal abnormalities or foetal deaths identified.

References:

Submission from Reilly Chemicals.

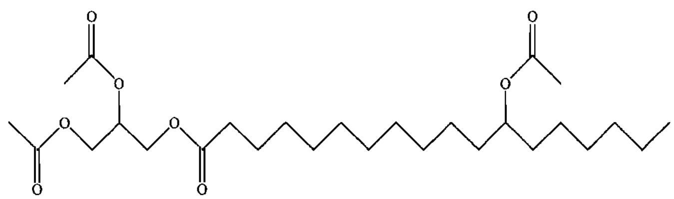
3. COMGHA (Glycerides, Castor-oil-mono-, hydrogenated, acetates)

3.1. Physico-chemical data

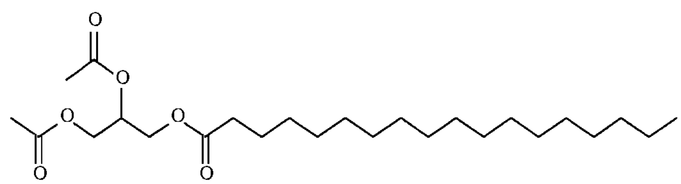
COMGHA is a mixture of two components A (Ca. 84%: 12-(Acetoxy)-stearic acid, 2,3-bis(acetoxy)propyl ester), and a minor component B (Ca. 10%: Octadecanoic acid, 2,3-(bis(acetoxy)propyl ester).

CAS Reg No :	736150-63-3 (COMGHA); Reg. No.: 330198-91-9 (component A); 33599-07-4 (component B)
Synonyms:	Acetylated monoglycerides of fully hydrogenated castor oil. Acetic acid esters of monoglycerides of fully hydrogenated castor oil. Octadecanoic acid, 12-(acetoxy)-, 2, 3-bis(acetoxy)propyl ester (main component).
Emperical formula:	$C_{27}H_{48}O_8$ (A) and $C_{25}H_{46}O_6$ (B)
Chemical structure:	

A



B



Molecular weight:	500.7 (A), 442.6 (B)
Melting point:	-21.5°C
Boiling point:	300°C at 1 atm (decomposition)
Vapour pressure:	< 2.8×10^{-4} Pa at 100°C
Solubility in water:	0.007 g/L
Log Kow:	6.4 (measured)
Purity:	About 94% (84% and 10% of the A and B components, respectively)
Impurities:	Octadecanoic acid, 12-acetoxy, 2-hydroxy, 3-acetoxypropyl ester (2%) Octadecanoic acid, 12-oxy, 2,3-bis(acetoxy)propyl ester (1.5%) Octadecanoic acid, 12-actyloxy, 2(acetoxy)-1,3-propanediyl ester (1.1%) Octadecanoic acid, 3-(acetoxy)-2-hydroxypropyl ester (1.0%) As (max 3 ppm), Pb (max 5 ppm), Hg (max 1 ppm), Cd (max 1 ppm)

3.2. Use

This plasticizer exhibits a performance similar to that of DEHP. It is approved in EU for use in food contact material. The intended primary use is in PVC (films, tubes, bottles, sealings, etc.), and the product may also find use in other polymers like polyolefines, styrenics, PET, etc. The product is recognised as a food packing material and evaluated by opinion of European Food Safety Authority (EFSA) 2004, 109, 1-26. Classified list 3. This product is notified as "new substances" in the context of 6th Amendment of Directive 67/548/EEC and listed in the European List of Notified Substances (ELINCS) as no. 451-530-8.

3.3. Exposure

No information has been found describing human exposure. Slightly lower leaching rate to sunflower oil (368 mg/dm^2) was found as compared to DEHP (Kristofferson 2005).

3.4. Metabolism

Quite detailed studies have been performed on absorption, distribution, biotransformation and excretion.. Main conclusion suggests that hydrolysis of the compound is incomplete and that a proportion of the administered dose passes through the gastrointestinal tract and is excreted unchanged.

3.5. Toxicity

Repeated dose toxicity

Similar effect as administering corn oil. The NOAEL is 3 ml/kg bw/day. 90 day oral toxicity. A 13 week toxicity in SD rats fed by gavage at 3, 8.5, and 20 ml/kg bw/day. The NOAEL was less than 3 ml//kg bw/day. An increased incidence of thymus atrophy was recorded in the highest dosed group but similar effects were seen in corn oil fed control group.

A second 13-week toxicity study in SD rats, where each group received diets containing o, 500 mg, 1600 mg or 5000 mg/mg/kg bw/day. The NOAEL was 5000/mg/kg/day. A chronic toxicity/ carcinogenicity study was not submitted.

The treatment of male rats with 8.5 ml/kg bw had no effect on palmitoyl-CoA activity whereas small but statistically significant increases in specific and total palmitoyl-CoA were observed in male rats given 20 mg/kg bw.

Induction on peroxisome proliferation: No marked effects on peroxisomal enzyme in the livers of male and female rats were observed after 13 weeks feeding study.

Mutagenity and genotoxicity

Negative. Non-mutagenic in gene mutation study with or without S9 mix. In vitro mammalian chromosome aberration test was negative. Non-clastogenic in the chromosome aberration test.

Reproduction/developmental toxicity

No studies submitted. A review of the toxicity of 12-hydroxy-octadecanoic acid, 12-acetoxyoctadecanoic acid and the systemic toxicity of acetic acid concluded no adverse effect have been reported of the two compounds but no data was available on the toxicity of 12-acetoxy-octadecanoic acid.

3.6. Human data

No information available on toxicity in humans.

3.7. Conclusion

Good information on fully functional replacement of DEHP is available. The compound migrates less than DEHP. Replaced 1:1 with DEHP.

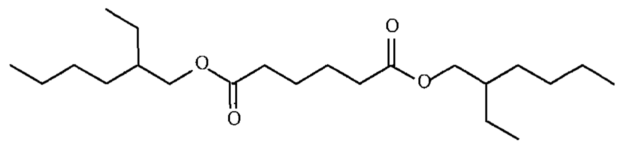
No original toxicity data were available. Based on the summary data it seems that the product is rather non-toxic. However basal toxicity on reproduction and immunotoxicity, sensitisation and chronic toxicity and cancer studies are missing.

References:
Submission from Danisco S/A.

4. DEHA (Di(2-ethylhexyl)adipate)

4.1. Physico-chemical properties

CAS Reg.	No: 103-23-1
Synonyms:	DEHA, di(2-ethylhexyl) adipate, DOA, dioctyl adipate
Empirical Formula:	$C_{22}H_{42}O_4$



Molecular weight:	370.57
Melting point:	-67.8°C
Boiling point:	214°C (0.67 kPa), 417°C (SIDS)
Vapour pressure:	8.5 x10^{-7} mm Hg at 25°C, 0.11 kPa (20°C), 0.32 kPa (200°C), 1.1 x 10^{-4} Pa at 20°C (SIDS)
Solubility in water:	0.78 mg/L (22°C)
Log Kow:	>6.11 (calculated), 8.0 (calculated)
Purity:	
Impurities:	0.01-0.02% adipic acid (purity >99%)

Leaching of plasticizers from food packing materials into especially fatty food has been studied a lot. In a Danish survey, plastic film on the market was tested for DEHA leaching to olive oil. Of the 49 investigated samples, 42 exceeded the action limit set at 4 mg (Breidendahl and Petersen 1998), cited in CSTEE opinion (1999).

4.2. Use

DEHA is a high production volume chemical that have an annual production and/or importation volumes above 1 million pounds in the U.S. DINP is used as a plasticizer in toys, vinyl flooring, wire and cable, stationery, wood veneer, coated fabrics, gloves, tubing, artificial leather, shoes, sealants and carpet backing.

4.3. Exposure

There has been uncertainty about the exposure of the general population. A survey covering 112 individuals established an intake of 2.7 mg/day (medium value). SCF evaluated the intake of DEHA in 2000 and concluded that the data showed DEHA intakes to be below the TDI of DEHA 0.3 mg/kg kg bw/ (SCF 2000, CSTEE 1999). No information has been found describing the exposure of children from PVC articles

4.4. Metabolism

DEHA is rapidly and completely absorbed from the gastrointestinal tract. After oral administration, DEHA is hydrolysed in the gastrointestinal tract to 2-ethylhexanol, mono(2-ethylhexyl) adipate and adipic acid. 2-ethylhexanol is also one of the metabolites of DEHP. Further details can be found in BUA, 1996.

4.5. Toxicity

Acute toxicity (Short term effects).
DEHA has very low acute toxicity. LD_{50} 7.4-45.0 g/kg bw.

Irritation
DEHA has been reported to be non-irritating or slightly irritating to the skin of rabbits. It fails to produce symptoms of a sensitising potential.

Repeated dose toxicity

A number of studies have shown DEHA to induce changes indicative of peroxisome proliferation in the liver. The peroxisomal effects of DEHA are moderate compared to those of DEHP. The metabolites appear to be the active compounds for the peroxisomal effects. 2-ethylhexanoic acid being the most active metabolite. There are no adequate performed studies, which allow a precise determination of a NOAEL for DEHA from subchronic or chronic studies. A recent study based on the draft protocol for the "Enhanced OECD Test guideline no 407" using oral administration of 0, 40, 200, and 1000 mg/day for 28 days showed a reduction in relative kidney weights at 200 and 1000 mg/kg/day (Miyata et al. 2006).

Genotoxicity
DEHA has not induced point mutation in *Salmonella typhimurium* or mouse lymphoma cells, sister chromatide exchanges in primary hepatocytes or Chinise hamster ovary cells, nor unscheduled DNA synthesis in primary rat hepatocytes.. DEHA did not cause chromosomal aberrations or micronuclei in primary rat hepatocytes. In one test on Chinese hamster ovary cells, an increase rate of chromosomal aberration was seen in the absence of a metabolic activation system; however, this study did not address cytotoxicity. DEHA has not induced micronuclei in mouse bone marrow cells or sex-linked recessive lethals in *Drosophila melanogaster.* In a dominant-lethal test in mice using intraperitoneal administration, a slight positive effect was seen. At the same time there was a reduction in the fertility index (not seen in orally studies), suggestion cytotoxicity rather than mutagenicity being the underlying cause for the dominant lethality (BUA, 1996). In an overall assessment of the test result, the CSTEE arrived at the conclusion that DEHA does not have a genotoxic potential (CSTEE 1999).

Carcinogenicity
Chronic toxicity and carcinogenicity study of several phthalic acid esters and compounds containing a 2-ethylhexyl moiety was conducted in Fischer 334 rats and B6C3F_1 mice (Kluwe 1986). In general, the toxic manifestation of the phthalic acid ester was closely correlated with their ester substituents. Although many of the phthalic esters possessed some carcinogenic activity, target sites for such effects were dissimilar, suggesting the absence of a common mode of action. In contrast, all of the 2-ethylhexyl-containing compounds studied possessed some hepatocarcinogenic activity, indicating that this moiety may have a propensity for causing hepatocarcinogenesis in mice. The 2-ethylhexyl compound that caused the greatest hepatocarcinogenic response in mice (DEHP), was also hepatocarcinogenic in rats.

Reproductive toxicity
Several studies show foetotoxic effect of DEHA (CSTEE 1999). A new detailed study using gavage administration of 0, 200, 400, or 800 mg/kg/day to pregnant rats, confirmed the foetotoxic effect. Maternal toxicity was seen at 800 mg/kg bw/day. The NOAEL for maternal toxicity was 400 mg/kg bw/day. The NOAEL was 200 mg/kg. DEHA induced a prolonged gestation period at 800 mg/kg. No antiandrogenic endpoints were affected. DEHA did not induce antiandrogenic effects similar to those of DEHP (Borch et al. 2002, Dalgaard et al. 2003, Borch et al. 2006). A recent study showed that combined perinatal exposure to a mixture of DEHA and DEHP did not exhibit more pronounced effects in the reproductive system than those observed in males receiving DEHP alone (Jarfelt et al. 2005). In the study of Mityata et al. (2006) a disturbance of the estrous cycle and increased ovarian follicle atresia were detected in the 1000 mg/kg group.

4.6. Human data

No information available on toxicity in humans.

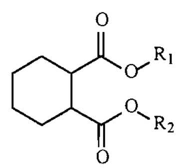
4.7. Conclusion.

DEHA does not show the specific toxicity on reproductive organs like DEHP on male pups after *in utero* exposure. A NOAEL of 200 mg/kg/bw for developmental toxicity and foetotoxicity can be established.

5. DINCH (1,2-Cyclohexanedicarboxylic acid, diisononylester)

5.1. Physico-chemical properties

CAS Reg. No.:	EU 166412-78-8, USA and Canada 474919-59-0, EC (ELINCS) number 431-890-2
Synonyms:	Hexamoll DINCH
Emperical formula:	$C_{26}H_{48}O_4$
Structure:	



R_1 and R_2 (not necessary identical) either mainly C_8H_{17} to $C_{10}H_{21}$ or C_9H_{19} isomers. In the case where R_1 and R_2 is C_9H_{19} isomersisomers it isis 10 % n-nonyl, 35-40 % methyloctyl, 40-45 % dimethylheptyl, 5-10 % methylethylhexyl

Molecular weight:	424.6
Melting point:	(liquid)
Boiling point:	240-250°C at 4 hPa
Vapour pressure:	< 2.8 x 10^{-4} Pa at 100°C
Solubility in water:	<0.02 mg/L at 25°C
Log Kow:	10.0 (calculated)
Purity:	>99.5%
Impurities:	< 0.05 % 1,2-Benzenedicarboxylic acid, dinonylester, branched and linear; < 0.5 % Dinonylether; < 0.1 % Nonanol, branched and linear derived from Oxo-process; < 0.5 % sum of Cyclohexanecarboxylic acid, nonylester, branched and linear and 2-Methylcyclohexanecarboxylic acid, nonylester, branched and linear

5.2. Use

DINCH was introduced recently and it is suggested as an alternative to DEHP "for sensitive applications". These include medical devices, such as blood tubes and packaging for nutrient solutions. The European producer has a capacity of 25,000 tpa but that is now going to be extended to 100,000 tpa.

5.3. Exposure

No information has been found describing human exposure. Using nutrition fluids for DINCH a 8-fold lower leaching into the fluids was found as compared to DEHP. Leaching of plasticizers from food packing materials into especially fatty food has been studied a lot.

5.4. Metabolism

After oral administration DINCH showed rapid but saturable absorption and extensive elimination 24 hours after dosing approximately 80% of the radioactivity is excreted, after 48 hours more than 90 % is excreted via urine and mainly via feces. Based on the amounts of radioactivity excreted in the bile and urine, the bioavailability of ^{14}C-1,2-Cyclohexanedicarboxylic acid di(isononyl)ester is estimated to be 5-6% at the high dose and 40-49 % at the low dose.

There is no indication of bioaccumulation. The characterisation of metabolites after oral and intravenous administration of DINCH indicates two main pathways: the partial hydrolysis of DINCH to the mono-isonyl ester followed by conjugation to glucuronic acid, which is the most ab Undant metabolite in bile, or the hydrolysis of the remaining ester bond to yield free cyclohexane dicarboxylic acid, the predominant urinary metabolite.

5.5. Toxicity

All toxicity studies presented were performed under GLP conditions according to OECD guidelines.

Irritation/sensitization
DINCH was demonstrated to be a non-irritant in both the rabbit skin test and rabbit eye test, and a non sensitizer in the Guinea pig maximization test.

Acute toxicity
DINCH has very low acute toxicity, the LD50 dose for DINCH in the rat is >5000 mg/kg bw after oral, and > 2000 mg/kg bw after dermal administration.

Repeated dose toxicity

28 day study
The 28 day toxicity study (dosing 0-600-3000-15,000 ppm or 0-64/66-318/342-1585/1670 mg/kg bw for males/females, respectively) was followed by a 14 days recovery period. The highest dose induced gamma-glutamyltransferase serum level and degenerated epithelial cells in the urine.

The NOAEL was 3000 ppm which relates to 318 mg/kg bw for males and 342 mg/kg bw for females.

90 day study
The 90 repeated dose toxicity study was performed with the doses 1500-4500-15000 ppm which relates to 107/128, 325/389, and 1102/1311 mg/kg bw for male/female animals, respectively.

There was no effect on mortality, clinical signs or haematology. Alterations were observed for clinical pathology including an increase in serum gamma-glutamyl transferase and TSH increase, in addition in urine blood and transitional epithelium cells were observed. The following pathological effects were present: an increase in liver weight, an increase thyroid weight, which was in line with the histology of showing hyperplasia/hypertrophy of the thyroid follicles. In the kidney alpha 2- microglobulin accumulation in the tubules was observed.

(NOTE the alpha 2-macroglobulin is considered specific for the rat and the mechanism thought not relevant for man). In the liver enzyme induction of phase I and phase II enzymes was observed. The increased gamma-glutamyltransferase and TSH value, increases in liver and thyroid gland, as well as the thyroid hypertrophy/hyperplasia suggest a common pathogenesis of enzyme induction process. This is not considered an adverse effect.

In the testes there was a significant increased mean relative weights in all 3 dose groups with no dose-response relationsip. Histopathologically there was no obstructive proces present in the male rete testis or other areas of the male reproductive system.

Based on kidney effects the NOAEL was 1,500 ppm (107.1 \mg/kg/day) in male and 4,500 ppm (389.4 mg/kg/day) in females. Also in the two generation study thyroid hyperplasia/trophy was observed with a NOAEL of 100 mg/kg/day.

Mutagenity and genotoxicity
DINCH has been evaluated for mutagenicity, both in bacterial (*Salmonella typhymurium/Escherichia coli* reverse mutation assay) and mammalian cell tests (In vitro mutation test in CHO cells), with negative results. It was non-clastogenic in tests conducted *in vitro* (chromosome aberration assay in Chinese hamster V79 cells) and *in vivo* (Micronucleus assay bone marrow cells mouse). DINCH is considered as non-genotoxic.

Carcinogenicity
In a two year combined chronic toxicity/carcinogenicity study (doses 40, 200, 1,000 mg/kg bw/day) also the thyroid was identified as target organ. Thyroid weight was increased in both sexes with follicular cell hyperplasia and the presence of follicular adenomas. The effect was considered due to secondary mechanisms via liver enzyme induction which is considered not relevant for humans. The NOAEL was 40 mg/kg in males and 200 mg/kg in females. Similar to the short term study transitional epithelial cells of the urinary tract were present in the urine. These were temporarily present and considered as adaptive as no histopathological lesions were observed in the kidneys at 12 and 24 moths.

Reproductive toxicity

Prenatal development studies

In prenatal toxicity study in rabbits DINCH was orally administered from day 6 to day 29 of gestation with doses of 100, 300, and 1,000 mg/kg bw/day. There were no signs for maternal toxicity, no influence on gestation parameters, no signs for developmental effects in pups or teratogenic effects. Soft tissue malformations were equal to control values. The NOAEL was determined at the highest dose investigated, 1,000 mg/kg bw/day.

In the prenatal development study in rats no effects were observed. The dosing of the mothers was form day 6 - 19 post coitum. The NOAEL was equal to the highest dose administered being 1,200 mg/kg bw/day

In a pre- and postnatal developmental study DINCH was administered orally to the mother animals from day 3 post coitum to day 20 post partum (750 and 1,000 mg/kg bw/day). Exposure of the offspring was via the mother animals during gestation and the lactation period until day 20 post partum. The offspring (all males and 3 females) was raised to days 100-105 post partum and then evaluated. Anogenital distance (AGD) and anogenital index (AGI, AGD divided by kg bw/) was measured at day 1 after birth., and sexual maturation was determined (testes descendance, balanopreputional separation, penis evaluation/inspection, sperm evaluation, and vaginal opening for females). Gross pathology was performed, and testes and epididymus were collected for histology.

The results indicated that there was no toxicity in F1 progeny with a NOAEL of 1,000 mg/kg/day. The AGD ($p<0.05$) and AGI ($p<0.01$) were significantly decreased in the male high dose group (1,000 mg/kg bw/day), respectively AGD 7% and AGI 8% below the control group. Also in females of the high dose group the AGI was significantly reduced by 8%. The AGI was also in females significantly ($p<0.05$) decreased.

The limited (7-8% change compared to controls), although significant alterations in the AGD and AGI are not considered of biological significance as other corresponding parameters were not affected like testes descendance, preputial separation, vaginal opening, testes weight and histology, and sperm parameters. Also in females the AGI was decreased to the same extent, contradicting the AGI to be an effect of impaired androgen dependent development. In addition, in the two generation study no effects were noted (but AGD and AGI not determined).

Two generation study

The two generation study was performed with continuous dietary administration (doses 0-100-300-1000 mg/kg bw/day). The animals remained in the same dosing group as their parents. Evaluated were sexual maturation of the F1 generation, and sperm parameters of the F0 and F1 generation. There were no effects on fertility and reproduction performance, and no substance related effects on the evaluated F1 and F2 generation. In the F0 parents an increase in gamma glutamyltransferase in females, decreased total bilirubin in females, and increased liver, kidney and thyroid weight in both males and females was observed. At the highest dose investigated (1000 mg/kg bw) For the F1 parents similar effects were noted including thyroid weight increase with thyroid hypertrophy/hyperplasia. The NOAEL for fertility and reproductive performance was 1000 mg/kg bw for both F0 and F1 parents, and 1000 mg/kg bw for developmental toxicity in F1 and F2 pups

5.6. Human data

No information available on toxicity in humans.

5.7. Conclusion

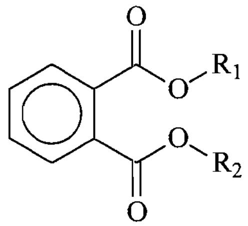
The toxicity of DINCH is lower than that of DEHP. DINCH also shows a different "hazard profile" from DEHP for reproductive toxicity and peroxisome proliferation. The magnitude of exposure resulting from differences in leaching of DEHP and DINCH from the plastics of interest, is less for DINCH. In addition, effects of DINCH are observed at higher exposure doses than DEHP.

References:
Submission from BASF.

6. DINP (di-iso-nonyl phthalate)

6.1. Physico-chemical properties

CAS Reg. No:	68515-48-0 and 28553-12-0 (different alcohol chains depending on production method)
Synonyms:	1,2-Benzenedicarboxylic acid, di-C8-10 branched alkylesters,
Empirical Formula:	$C_{26}H_{42}O_4$ (average)
Structure:	



R_1 and R_2 (not necessary identical) either mainly C_8H_{17} to $C_{10}H_{21}$ or C_9H_{19} isomers. In the case where R_1 and R_2 is C_9H_{19} isomers it is 10 % n-nonyl, 35-40 % methyloctyl, 40-45 % dimethylheptyl, 5-10 % methylethylhexyl

Molecular weight:	420.6 (average)
Melting point:	-40 to -54°C
Boiling point:	424°C
Vapour pressure:	6×10^{-5} Pa at 20°C
Solubility in water:	0.6 µg/L
Log Kow:	8.8
Purity:	These products are mixtures of different composition and can contain up to at least 40 different substances
Impurities:	DINP is not a pure substance, but a complex mixture containing mainly C9-branched isomers: iso-Nonanol ca. 0.04%, iso-nonylbenzoate ca. 0.03%, n-butyl-iso-nonyl phthalate ca. 0.1%, water 0.02-0.03%.

6.2. Use

There are currently four producers of DINP in EU. Approximately 95% of DINP are used in PVC as a plasticizer. (RAR EU 2003). It has limited use in food packing material and is not used in medical products (CSTEE 2001). DINP is used as a plasticizer in toys, vinyl flooring, wire and cable, stationery, wood veneer, coated fabrics, gloves, tubing, artificial leather, shoes, sealants and carpet backing.

6.3. Exposure

The estimated maximum combined total daily intake for an occupationally exposed adult is 1.12 mg/kg bw/d. For non-occupational exposed adults and children a maximum exposure of 20 µg/kg bw/d is estimated. These estimates are based on DINP measurements in several environmental media and consumer products (ECB 2003). From urinary DINP metabolite concentrations median daily intakes of approx. 0.2 µg/kg bw/d have been calculated for the general population with maximal values of 20 µg/kg/d (David 2000; Kohn 2000; Wittassek submitted).

Infants (0.5-3 years old)
Based on probabilistic estimation the maximum total daily intake from consumer sources is 0.25 mg/kg bw/d and via the environment 0.16 mg/kg bw/d. (combined exposure 0.41 mg/kg bw/d) (ECB 2003).

6.4. Metabolism

In rats DINP is readily absorbed and approximately 50% of an oral DINP dose is excreted renally, mainly as oxidised metabolites of the monoester mono-iso-nonyl phthalate (MINP) (ECB 2003; McKee 2002; Silva 2006a). These oxidised metabolites have also been identified in humans (Koch in press b; Silva et al. 2006a, 2006b). More than 40% of an applied DINP dose to a male volunteer was recovered in urine in form of oxidised MINP-isomers with hydroxy (20%), oxo (11%) and carboxy (11%) functional groups (Koch in press a). The simple monester MINP urinary excreted accounted only for 2% of the dose. Elimination was at least bi-phasic and elimination half-lives in the second phase (beginning 24h post dose) were 12 hours for OH-MINP and oxo-MINP and 18 hours for carboxy-MINP. Further metabolites may be breakdown products through α- and β-oxidation of the alkyl side chain and those with more than one functional groups through oxidation (Koch in press a; Silva 2006a).

6.5. Toxicity

Acute toxicity
Upon single exposure, DINP has a low acute toxicity by all routes of administration.

Repeated dose toxicity
The liver is a target for chronic toxicity and a NOAEL of 88 mg/kg bw/d can be assumed on hepatic biochemical and histopathological findings. In 2001 CSTEE expressed an opinion on DINP-RAR and disagreed with a use of a NOAEL of 88 mg/kg/d. CSTEE support the use of spongiosis hepatis in rat as the critical effect for DINP, applying a benchmark dose of 12 mg/kg/d. Two studies show spongiosis hepatica with a benchmark dose 12-15 mg/kg/d (Aristech, 1994; Moor, 1998 cited from CSTEE 2001).

For kidney effects, a NOAEL of 88 mg/kg bw/d based on increase kidney weights can be assumed.

Mutagenity and Genotoxicity
DINP is not mutagenic *in vitro* in bacterial mutation assays or mammalian gene mutation assays (with or without metabolic activation) and is not clastogenic in one cytogenic assay on CHO cells and in one *in vivo* assay on bone marrow cell of Fisher rats. This suggests that DINP is not genotoxic.

Carcinogenicity
In chronic/carcinogenicity studies, DINP was found to induce significant excess of liver neoplasia in rats and mice. This is explained by peroxisome proliferation mode of action. DINP in two studies increased the mononuclear cell leukaemia in Fisher rat. IARC has classified this leukaemia of no relevance for human.

DINP induce kidney tumours in male rats but this 2u globulin induced tumours is not considered as relevant to humans.

Reproductive/developmental toxicity
In mice, a very high dose (>5g/kg bw/d lead to a decrease in testicular weight with abnormal/immature sperm forms and uterus/ovaries atrophy in a 13-week study. A NOAEL of 276 mg/kg bw/d for testicular effects can be assumed in a 104-week chronic rat study based on a reduced testicular weight at 742 mg/kg.

In the developmental studies, visceral and skeletal variations increased on litter basis at 1,000 mg/kg/d, leading to a NOAEL of 500 mg/kg bw/d. A decrease of mean offspring kg bw/ was observed following parenteral administration of DINP in the one and two-generation study from the lowest dose tested (LOAEL of 159/mg/kg bw/d).

DINP is not estrogenic *in vitro* but recent studies after perinatal exposure indicated that that male displayed female like areolas/nipple retention and that incidence of reproductive malformation was slightly but significantly increased (7.7% versus 91% with DEHP) Gray et al. (2000). (The reproductive effect of DINP is similar to the profile shown for DEHP but DINP is only half or less potent as DEHP. There is an increasing use of DINP but the reproductive toxicity of all the isomers is not well investigated (CSTEE 2001).

6.6. Human data

No information available on toxicity in humans.

6.7. Conclusion

The reproductive seffect of DINP indicate a similar hazard profile (except age) as shown for DEHP, but DINP is only half or less potent as DEHP. The mechanism of action is an effect on steroidogenesis of testosterone in the fetal male rat like shown by DEHP. CSTEE (2001) has previously recommended that the NOAEL effect is lower than the one reported in the RAR if using the spongiosis hepatis as the critical endpoint. This is seen in doses of 12-15 mg/kg/d.

References:

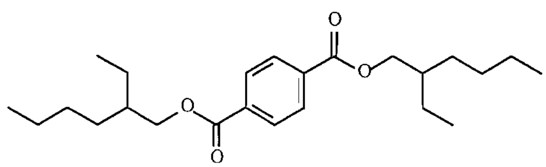
ECB. European Union Risk Assessment Report for 1,2-benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich and di-"isononyl" phthalate (DINP) (Final Report 2003). Doc. No. European Chemical Bureau, 2003.
Koch HM and Angerer J. Di-iso-nonylphthalate (DINP) metabolites in human urine after a single dose of deuterium-labelled DINP. *Int J Hyg Environ Health* in press a
Koch HM, Muller J and Angerer J. Determination of secondary, oxidised di-iso-nonylphthalate (DINP) metabolites in human urine representative for the exposure to commercial DINP plasticizers. *J Chromatogr B Analyt Technol Biomed Life Sci* in press b, doi:10.1016/j.jchromb.2006.09.044
McKee RH, El-Hawari M, Stoltz M, Pallas F and Lington AW. Absorption, disposition and metabolism of di-isononyl phthalate (DINP) in F-344 rats. *J Appl Toxicol* 2002, 22, 293-302.
Silva MJ, Kato K, Wolf C, Samandar E, Silva SS, Gray EL, Needham LL and Calafat AM. Urinary biomarkers of di-isononyl phthalate in rats. *Toxicology* 2006a, 223, 101-12.

Silva MJ, Reidy JA, Preau JL, Jr., Needham LL and Calafat AM. Oxidative metabolites of diisononyl phthalate as biomarkers for human exposure assessment. *Environ Health Perspect* 2006b, 114, 1158-61.

7. DEHT (Di(2-ethylhexyl) terephtalate)

7.1. Physico-chemical properties

CAS Reg. No:	6422-86-2
Synonyms:	1,4-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester; dioctylterephthalate (DOTP); Eastman Plasticizer 168.
Emperical formula:	$C_{24}H_{38}O_4$
Molecular weight:	390.56
Structure:	



Melting point:	-48°C
Boiling point:	363°C (383 enl IUCLID)
Vapour pressure:	28.5 hPa at 25°C, 1013 hPa at 398°C
Solubility in water:	0.4 µg/L (well water), 0.35-1.5 mg/L (sea water)
Log Kow:	5.72 (well water), 5.26 (sea water)
Purity:	98.5%
Impurities:	<2% w/w 2-ethylhexyl methyl terephthalate

Information on stability in water is given (in section 3.2.1 of IUCLID set) and the calculated rate constants for hydrolysis. GC-ECD method for parent compound determination (e.g. page 50 of IUCLID)

7.2. Use

DEHT is a high production volume chemical and is annually produced in volumes above 50 million pounds in the U.S.

DEHT is used as a general purpose, low-volatility plasticizer for polyvinyl chloride and other polymeric materials. It is used in a wide range of applications including toys, childcare articles and other consumer products, transportation and beverage closures. According to IUCLID Data Set, the production volume in 1998 was 25000 – 50000 tonnes in the US.

7.3. Exposure

DEHT production uses a closed system. Occupational exposure could occur when the chemical is put into drums or during quality control. It is said that minimal consumer exposure is expected based on limited use in consumer products and low leaching of the compound out of the polymer matrix in its major use as plasticizer.

7.4. Metabolism

<u>In vitro</u>: The metabolic hydrolysis rate of DEHT; determined by the formation of free 2-ethylhexanol (2-EH) was studied with rat intestinal homogenate ($t_{1/2}$ was 53 min; and stoichiometry at termination showed about 2 mol of 2-EH per mol DEHT, indicating complete hydrolysis to terephthalic acid (TPA). This was in contrast to DEHP (with $t_{1/2}$ of 13 min and a yield of 1.2 mol of 2-EH per mol DEHP) indicating it forms a stable monoester:

<u>Oral study</u>: Absorption and metabolism were studied for DEHT (^{14}C labelled) mixed with corn oil and administered by gavage in a single dose of 100 mg/kg of kg bw/ to 10 adult male SD rats. About 93 % of the total radioactivity was recovered, most of it in the faeces (56.5%), and urine (31.9%), and 3.6% was expired as CO_2. The mean amount of unchanged radioactive DEHT recovered in the faeces was 36.6% and the percentage of the total DEHP dose recovered in the urine, as unlabeled TPA, was 50.5%. In total 91.7 % of the dose can be accounted for as either unchanged DEHT (in faeces), unlabeled TPA (in urine) or exhaled CO_2. This balance sheet thus limits the amount of mono(2-ethylhexyl) terephthalate (MEHT), and its metabolites to a maximum of 9.3 % of orally administered dose: After 24 hours more than 95%of the radioactivity was excreted [Barber et al. 1994].

Apparently; DEHT is not readily absorbed from the GI tract upon oral exposure; and extensively hydrolyzed to TPA and 2-EH (before and after absorption) and it is rapidly excreted. This contrasts to the metabolite profile of the ortho-phthalate DEHP which primarily undergoes hydrolysis to form the monoester (MEHP).

7.5. Toxicity

Acute toxicity

Acute toxicity data are mainly reported for rats and, mice. LD50 was >5000 mg/kg and 3200 mg/kg bw in oral studies and >20 ml/kg for dermal toxicity in guinea pigs

Repeated dose toxicity
4-5 studies conducted; some according to GLP. Groups of male and female rats were fed diets containing DEHT at 0.1 up to 1% and 2.5% w/w for up to 90 days:
[a] SD rats 90 day (GLP) study: NOEL was 0.5% or 277 and 309 mg/kg bw for males and females, respectively; the NOAEL was 1% or 584 and 617 mg/kg bw for males and females, respectively. Slight increases in relative liver weight (max about 11%) were seen at the 1% dose level. No adverse effects on the testes were found at any dose [Barber & Topping 1995].

[b] Fisher 344 rats 21 day (GLP) study: NOEL was 0.5% or 487 and 505 mg/kg bw for females and males respectively; the NOAEL was 1.2% or approx: 1000 and 1100 mg/kg bw for males and females, respectively. DEHT caused only slight peroxisome proliferation at 2.5%, whilst DEHP caused a moderate increase at 1.2% and a marked increase at 2.5% in this study [Topping et al. 1987]. The effect seen at the 2.5% exposure level was believed to be secondary to significant decreases in food intake and body weight reduction.

Two other repeated dose studies, one in SD rats with oral feeding at levels of 0.1 and 1% for 2 weeks, the other with inhalation (6h per d for 10 days) of 46.3 mg/m^3 revealed no signs of toxicity; the NOEL for these studies were the highest tested doses.

Mutagenity and Genotoxicity
No evidence for genotoxicity was found in assays assessing mutagenicity, *i.e.* gene mutation in bacterial (Ames test) or mammalian (CHO / hgprt) system. DEHT did not induce chromosomal aberrations in mammalian cultured cells with or without an exogenous metabolic activation system. The results for mono(ethylhexyl)terephthalate (MEHT) in the Ames assay were also negative [Barber 1994].

Carcinogenicity
Data from a chronic 104 weeks oral study indicate a NOEL for carcinogenicity of 12000 ppm (highest dose tested), equivalent to 666 mg/kg/day in males and 901 mg/kg/day in females.

The NOEL for chronic toxicity in the study was 1500 ppm equivalent to 79 mg/kg/day in males and 102 mg/kg/day in females.

Reproduction/ developmental toxicity
In a two generation reproductive toxicity study following OECD guideline 416, DEHT was given to 30 male and 30 female SD rats at doses of 0, 0.3, 0.6 and 1% in the diet (approx. 0, 150-200; 300-400; 500-700 mg/kg/day for males, and 0, 250-300, 500-600, 800-1000 mg/kg/day for females). The F0 animals received DEHT for at least 70 days before mating and until termination; the F1 generation received diets following weaning (following PND 22) and for at least 70 days before mating. Reproductive parameters were unaffected by DEHT. Mean maternal kg bw/s were reduced in the 1% group throughout gestation and lactation and throughout the F1 generation. No critical histopathological changes observed: The NOAEL for reproductive toxicity was concluded to be 1% in the diet.

<u>Oral developmental toxicity</u>

Study 1 following OECD guideline 414: Groups of 25 pregnant SD rats received DEHT doses of 0, 0.3, 0.6 and 1% in the diet (approx. 0, 226, 458, or 747 mg/kg/day) from GD 0 to GD 20. Uteri and contents were excised by caeserean section and examined (fetuses, implantation sites): No evidence of embryotoxicity, fetotoxicity and no effect of treatment on the number of viable foetuses. No visceral or skeletal anomalies attributed to treatment. Changes in maternal kg bw/ were seen at the highest exposure level and the NOAEL for maternal toxicity was 0.6 % (458 mg/kg/day); the NOAEL for developmental tox was 1% (747 mg/kg/day).

Study 2: 10 Controls and 8 pregnant SD rats received DEHT from GD14 to PND3 by gavage at 0 and 750 mg/kg bw (dose adjusted based on individual maternal weight changes throughout dosing period), and their male offspring were examined for several parameters of demasculinization: No changes in AGD, testes weight, testes descent, testes lesions, presence of areolas/nipples or vaginal pouches, reproductive organs weights, reproductive malformations or mating behaviour were noted. In contrast, DEHP also assessed in the same study, yielded adverse effects at this dose (750 mg/kg bw) [Gray et al. 2000].

Study 3 following OECD guideline 414: Groups of pregnant CD mice received DEHT doses of 0, 0.1, 0.3 and 0.7% in the diet (approx. 0, 197, 592, or 1,382 mg/kg/day) from GD0 to GD18. Changes in maternal weights were seen in the mid and high exposure animals, and the NOEL for maternal toxicity was 0.1% (197 mg/kg bw); the NOEL for developmental toxicity was 0.7% (1,382 mg/kg).

7.6. Human data

There are two small human studies reported, both with dermal application of DEHT, one to test primary dermal irritation, the other on skin sensitization. Under the conditions of the study DEHT was found to be non-irritating and did not elicit evidence of sensitization. No other human studies.

7.7. Conclusion

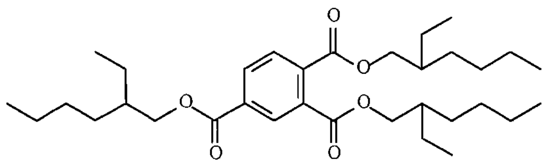
DEHT is not genotoxic (like its isomeric relative DEHP). DEHT is less active in the induction of peroxisome-proliferation in rats than DEHP, and this is explained by the smaller amounts of monoester produced during DEHT metabolism. At doses where DEHP, BBP and DINP all altered sexual differentiation, DEHT was inactive. (DEHP, BBP were of equivalent potency, DINP was about an order of magnitude less active).

References:
Submission from Eastman Chemical Company.

8. TOTM (Trioctyltrimellitate)

8.1. Physico-chemical properties

CAS Reg. No:	3319-31-1
Synonyms:	Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate, trioctyl trimellitate; tri(2-ethylhexyl) trimellitate (TEHTM); trioctyl benzene-1,2,4-tricarboxylate; 1,2,4-bezenetricarboxylic acid, trioctyl ester.
Emperical Formula:	$C_{33}H_{54}O_6$
Structure:	



Molecular weight:	546.8
Melting point:	-50°C (-35 in IUCLID)
Boiling point:	283°C at 4 hPa
Vapour pressure:	5.6 Pa at 20°C
Solubility in water:	0.13 (0.00039) mg/L at 25°C
Log Kow:	5.94 (4.35) at 25°C
Purity:	
Impurities:	

In the dossiers no method of determination of substance and metabolites were presented. The open literature gave two papers in which HPLC methodology were applied for TOTM analysis (Christensson et.al. 1991, Kambia et.al. 2001). No methods for the metabolites are available, however most probably DEHP methods are applicable.

8.2. Use

The production volume in Japan is about 20.000 tonnes/year and there are 5 manufacturers in Japan. Estimated global production is 40,000-100,000 tonnes/year. TOTM is mainly used as a plasticizer for PVC electrical cables and wire. In medical devices TOTM is used as a PVC plasticizer in various infusion equipments.Trimellitate plasticizers are the altemative for phthalate plasticizers when high temperature applications and low volatility are of importance. The end products include oil resistance products, gasoline hoses, rain shoes, gasketing, and vehicle engine wires. TOTM has unique low leaching properties and extraction resistance properties that are required for dishwasher gaskets, medical tubing and photograph storage.

8.3. Exposure

TOTM is produced and used in closed systems and therefore the occupational exposure is limited in the case of sampling and maintenance at the production facilities. Moreover, the exposure time is very short. The major route of occupational exposure is inhalation and dermal. TOTM is relatively difficult to extract from the polymeric matrix which lowers the consumer (patient) exposure.

8.4. Metabolism

Absorption and metabolism were studied for TOTM (14C labelled) mixed with corn oil and administered by gavage in a single dose of 100 mg/kg of kg bw/ in 4 male SD rats. About 75% of the dose was excreted unchanged in the faeces, 16% in the urine as metabolites and 1.9% was expired as CO2. Radioactivity was excreted in the faeces as unchanged TOTM (85% of the faecal radioactivity) mono and di(2-ethylhexyl)trimellitate (MOTM and DOTM), and as unidentified polar metabolites. Metabolites in the urine were identified as MOTM nabd metabolites of 2-ethylhexanol. Less than 0.6% of the dose remained in the tissues (SIDS Initial Assessment Report for 13th SIAM, 2001).

8.5. Toxicity

Acute toxicity

Acute toxicity data are mainly reported for rat, mice and rabbits. LD50 was >2000 mg/kg and 3200 mg/kg bw in oral or IP administration in rats (Ministry of Health and Welfare, Japan 1996).

Repeated dose toxicity

Oral administration of TOTM in the diet to groups of 5 male and 5 female Fisher 344 rats at the level of 0, 184, 650, 1826 mg/kg bw/day for 28 days. There were no statistical significant differences in kg bw/ between the control and the exposed groups. There was a significant difference in between the control and exposed groups in the following absolute and relative liver weights, serum albumin and cholesterol levels. Liver biochemistry (palmitoyl CoA oxidation and catalase activity were induced) revealed statistically significant differences between treated and control groups. The NOAEL was 184 mg/kg (CMA 1985)/day.

In the second study the NOAEL was 1000 mg/kg/day; not all the informations are available (Ministry of Health and Welfare, Japan 1996).

The third study was the OECD preliminary reproduction study. Administration was by gavage at the doses of 100, 300 and 1000 mg/kg/day. The decrease of spermatocytes and spermatides in males was observed at 300 and 1000 mg/kg/day doses by histopatohological examinations. The NOAEL was 100 mg/kg for males and 1000 mg/kg/day in females (Ministry of Health and Welfare, Japan 1998).

In a non GLP compliance study rats were exposed to TOTM and DEHP (28 days, 0.2%; 0.67%; 2.00%). The data demonstrated the same spectrum of morphological and biochemical changes in the livers of rats exposed to TOTM as did DEHP. TOTM, however, was much less potent in its action, with a dietary level of 2%, causing less peroxisome proliferation and enzyme induction than 0.67% DEHP (Hodgson J. Toxicology and Industrial Health 1987).

Adult male rats receiving TOTM intraperitoneally for seven days exhibited no significant changes in the activities of hepatic aminopyrine-N-demethylase, aryl hydrocarbon hydroxylase or glutathione-S-transferase or in glutathione contents. However, except for the glutathione level, the DEHP shoved significant increases in the activities of these particular enzymes (Rathinam K. et.al.1990).

Mutagenity and genotoxicity

One GLP level study for Ames test was carried out and several (4 to5) non GLP compliant studies exist. In the GLP compliant study TOTM did not induce gene mutation in bacterial system and chromosomal aberration in mammalian cultured cells with or without an exogenous metabolic activation system (Ministry of Health and Welfare, Japan 1996).

Reverse gene mutation assay was conducted by OECD TG 471 and 472 using preincubation method TOTM was not mutagenic in Salmonella TA100, TA1535, TA 98, TA1537 and E.coli WP2 uvrA at concentration of up to 5000 µg/plate, with or without tan exogenous metabolic activation (Ministry of Health and Welfare, Japan 1996).

Chromosomal aberration test by OECD TG 473 was conducted in cultured Chinese hamster lung cells. Structural chromosomal aberrations and polyploidy were not induced to a max conc. of 5,0mg/ml on continuous treatment (Ministry of Health and Welfare, Japan 1996).

Carcinogenicity

No data available.

Reproduction/developmental toxicity

Gavage study in SD rats conducted at doses of 100, 300 and 1000 mg/kg/day (male 46 days, females from 14 days before mating to day 3 of lactation) of TOTM. Histopathological examination of testes revealed decreased spermatocytes and spermatids in males of the 300 and 1000 mg/kg/day groups. No effects of TOTM were detected general appearance, kg bw/, food consumption autopsy findings and weight of repro organs of both sexes or on histopathological examination of the ovary. On the basis of this observation the NOAEL for males is 100 mg/kg/day and 1000 mg/kg/day in females (Ministry of Health and Welfare, Japan 1998).

No influence of TOTM was detected regarding reproduction ability, organ weights or histopathological appearance of the ovaries, delivery or maternal behaviours of dams. No effects were seen on viability, general appearance, of weight or autopsy findings of offspring. The NOAEL for repro/developmental toxicity is considered to be 100 mg/kg/day for males, 1000 mg/kg/day for females and 1000 mg/kg/day for offspring (Ministry of Health and Welfare, Japan 1996).

8.6. Human data

The leaching of plasticizers from blood line was studied in 11 patients. During the treatment the plasma level of DEHP rose from 0.1 microg/ml (<0.05-0.17, n=11) to 0.7 microg/ml (0.30-1.6, n=11). When patients were changed to tubing containing TOTM, the concentration of DEHP was below or close to the detection limit (LOD 0.5 microg/ml) and TOTM could not be detected (LOD 0.5 microg/ml) (Christersson et.al. 1991).

The circulating concentrations of DEHP and TOTM resulting from the release from dialyzer tubes were estimated using an HPLC. A DEHP quantity of 122.95+/- 33.98 mg (n=10) was extracted from tubing during a single dialysis session (4h). By using TOTM-DEHP 1:1 mixture, 41.80+/- 4.47 mg of DEHP and 75.11+/-25.72 mg of TOTM were extracted (Kambia et.K. et al. 2001). (1-2) 139-146.)

Two hundred and three human volunteers were tested for evidence of sensitization to several plasticizers following 3 weeks of dermal application three times a week. Slight erythema was observed in four individuals exposed to TOTM, two of which resolved within 96 h and one that occurred only after 96 h (David et.al.2003).

8.7. Conclusion

TOTM has a low acute toxic potential. Based on the data available TOTM seem to have low metabolic transformation capacity and no major single water soluble metabolite can be identified. This may partially explain the low liver toxicity of the compound. No clear toxicological mode of action can be identified. However, the spectrum of some morphological and biochemical changes in rat liver were the same in TOTM and DEHP but the degree of damage was by far lower in TOTM exposed animals than in DEHP. The overall NOAEL can be set to 100 mg/kg in male based on the damage reported in testes in animals.

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Submission from Polynt S.p.A

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Hexamoll® DINCH

Comparison of Hexamoll DINCH to
Palatinol® AH (DOP, DEHP) and Palatinol N (DINP)

August 2008

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Summary

Hexamoll DINCH, the ester of cyclohexanedicarboxylic acid and C9-alcohols, has been developed for applications considered as especially sensitive relating to the much-discussed toxicological properties of phthalates. In particular these applications include „human contact" applications e.g. medical products, toys and food packaging. Compared to standard phthalates Hexamoll DINCH offers an improved toxicological profile. For processing of flexible PVC compounds containing Hexamoll DINCH in most cases only minor changes have to be made as far as the formulation and processing parameters are concerned.

Physical properties of Hexamoll DINCH as well as simple flexible vinyl formulations are compared to well known general purpose plasticizers Palatinol AH (DOP, DEHP) and Palatinol N (DINP). Also the current toxicological status is given.

Some of the physical properties of Hexamoll DINCH differ as compared to the standard phthalates. The solution temperature (temperature at clear point) is higher compared to DOP and Palatinol N. The higher the solution temperature the poorer is the gelling or fusion behavior. At the same time a higher solution temperature results in an improved viscosity stability of plastisols on storage. The viscosity of the pure plasticizer is lower than that of DOP and Palatinol N respectively. The lower the viscosity the easier the handling of the plasticizer and the lower the initial plastisol viscosity.

The plasticizer efficiency based on Shore-A hardness is almost 10% poorer than that of DOP and Palatinol N. The low temperature behavior of Hexamoll DINCH is better than with the compared phthalates. The volatility of Hexamoll DINCH is in-between DOP and Palatinol N.
The dry blending behavior of Hexamoll DINCH differs substantially from both standard phthalates. In high-speed mixers Hexamoll DINCH does not dry as fast. That is why an increased blending temperature is suggested.

Apart from the need for a different treatment of formulating and processing, we received well-balanced properties with Hexamoll DINCH as compared to the standard phthalates DOP and Palatinol N.

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1. Plasticizers - typical values

parameter	unit	Hexamoll DINCH	DOP	Palatinol N
density	g/cm³	0,947	0,984	0,972
viscosity	mPa*s	48	79	72
refractive index	n_D^{20}	1,462	1,487	1,485
Acid number	mg KOH/g	0,04	0,02	0,04
Pt/Co color		5	5	5
Water content	%	0,02	0,02	0,03
Solution temperature (at clear point)	°C	151	124	132

- The density of Hexamoll DINCH is approx.2-3% below that of DOP and Palatinol N.
- The viscosity is significantly lower than of DOP and Palatinol N, which is favorable for handling and plastisol applications.
- The higher solution temperature of Hexamoll DINCH indicates the need for higher processing temperatures / longer time.

2. Tests on flexible PVC

2.1 Formulations

	A	B	C	D	E	F	G	H
Solvin 271 SP	100	100	100	100	100	100	100	100
Plasticizer	30	40	50	60	70	80	90	100
Lankromark LZB 753	2	2	2	2	2	2	2	2

2.2 Sample preparation

2.2.1 Dry Blending (mixing)

A laboratory high-speed mixer (Henschel FM/KM) was used for dry blending. The PVC was filled into the mixer and heated to 50°C at 1500 rpm. Then the plasticizer was added within 1 minute at reduced rpm of 750. The speed was increased again to 1500rpm until the mixture dried (amperage drop). Then the stabilizer was added with a syringe and the mixer speed was brought to 2500 rpm until the target temperature was reached. The dry blend was cooled in the cooling mixer and bagged at 30°C.

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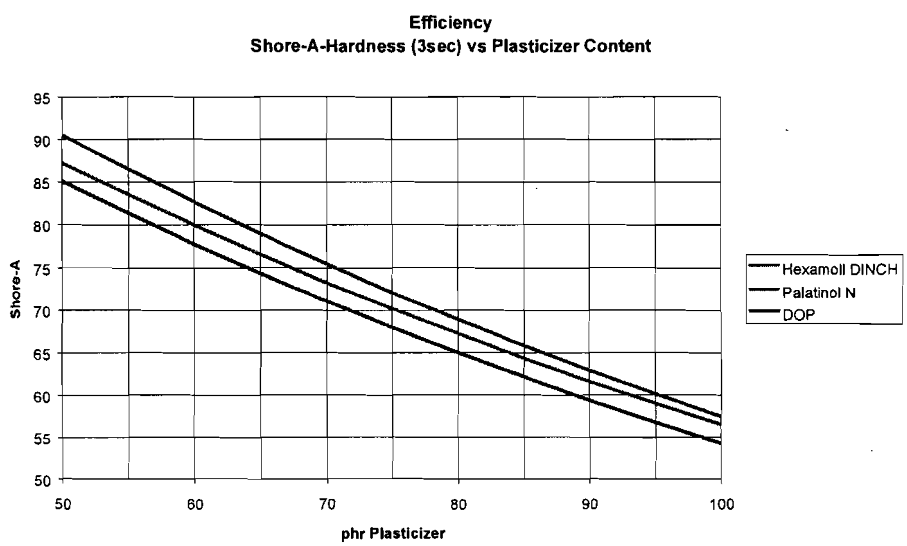
2.2.2 Milling and pressing

The dry blends were milled for 5 minutes on a Collin laboratory two-roll mill at appropriate temperatures as shown in the table below.

Milling temperature	A	B	C	D	E	F	G	H
DOP	180	180	180	170	170	165	165	155
Palatinol N	180	180	180	170	170	170	170	160
Hexamoll DINCH	180	180	180	170	170	170	170	160

The milled sheets were pressed two needed thickness in a Collin laboratory press for 3 minutes at 10°C above the milling temperature.

2.3 Plasticizer efficiency – Shore hardness



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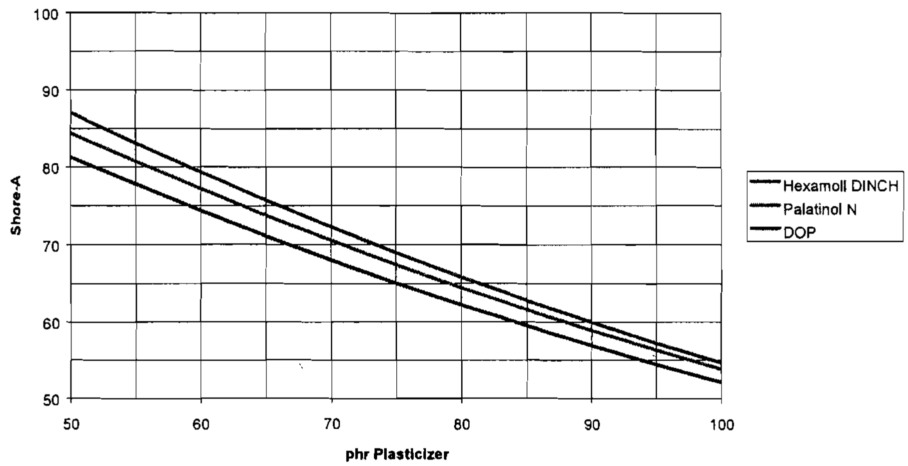
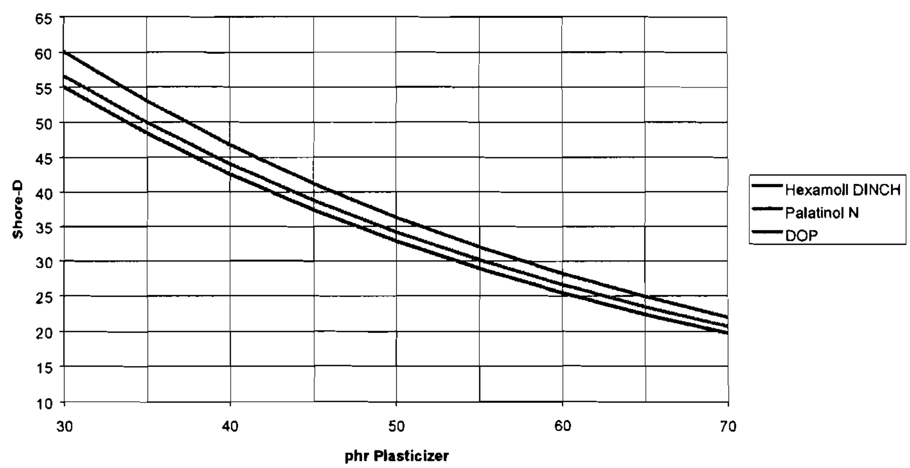
Efficiency
Shore-A-Hardness (15sec) vs Plasticizer Content



Efficiency
Shore-D-Hardness (3sec) vs Plasticizer Content



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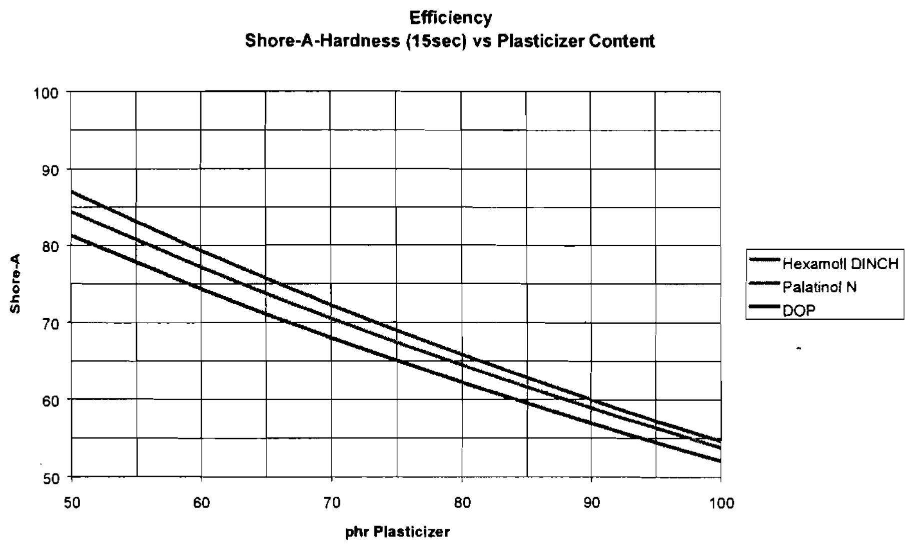

As can be seen from the Shore hardness graphs the efficiency of the three plasticizers is different. In order to obtain the same hardness the phr of plasticizer is to be adjusted for efficiency (based on Shore-A) with the efficiency factor compared to the DOP formulation:

DOP	: 1
Palatinol N	: 1.055
Hexamoll DINCH	: 1.10

These factors hold true in the range of Shore-A 70. Any other Shore-hardness and corresponding plasticizer concentration can be obtained from above diagrams.

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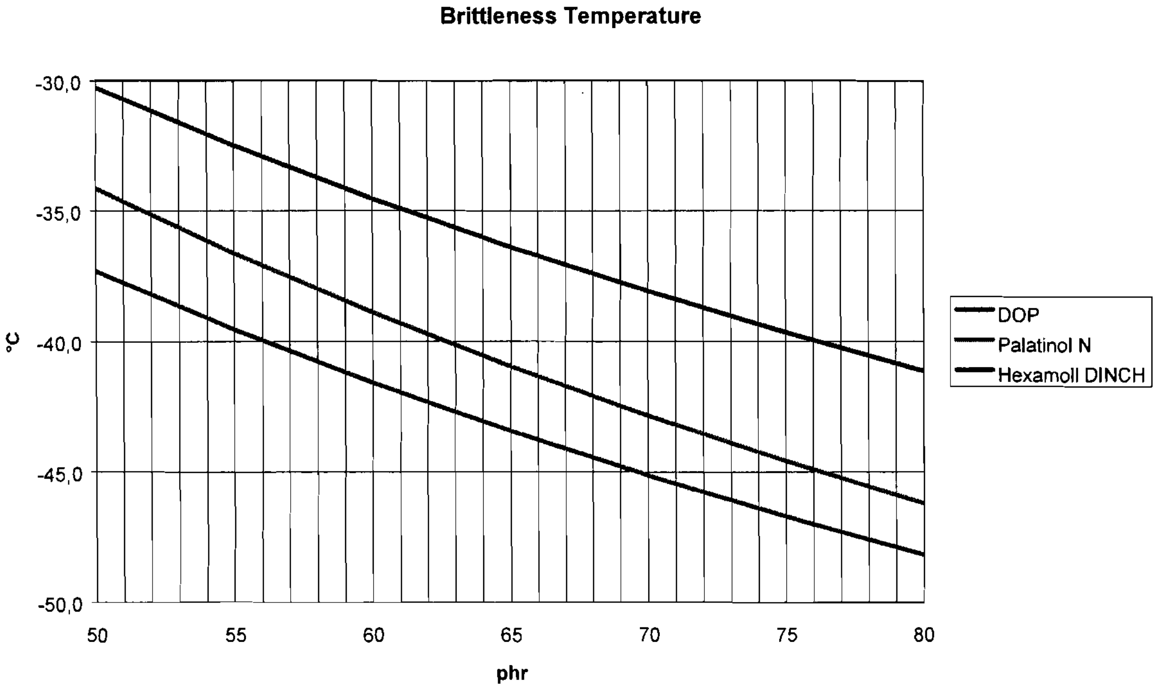
2.4 Brittleness temperature



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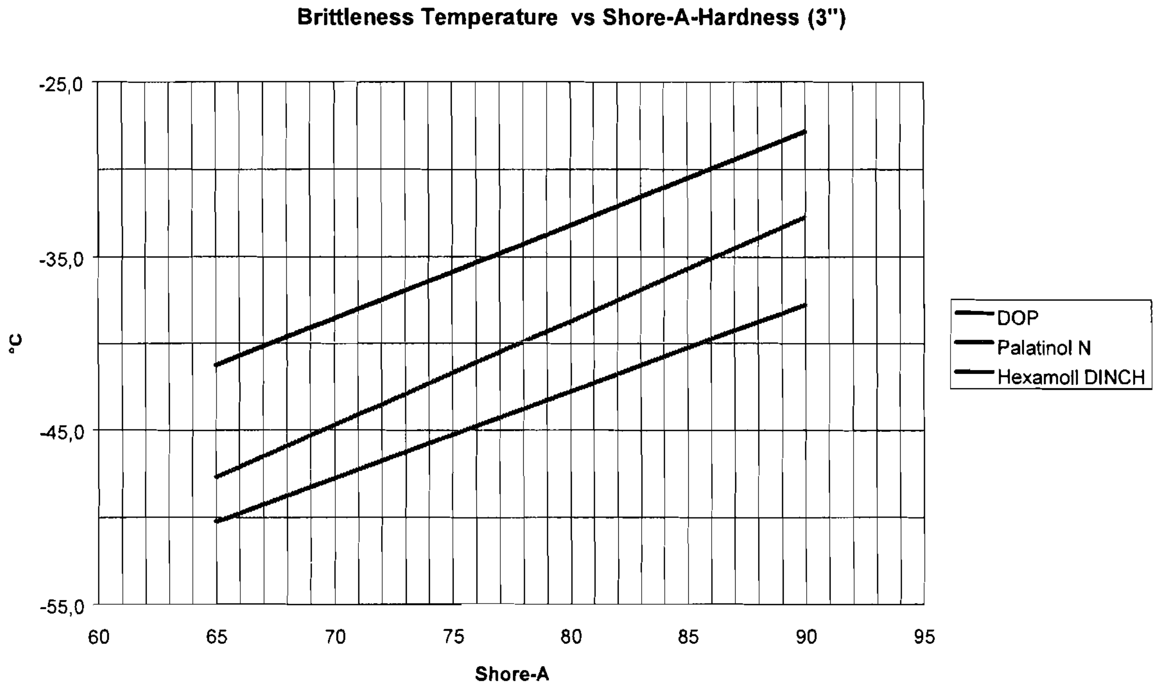

Hexamoll DINCH has excellent low temperature properties as compared to DOP and Palatinol N. This can be demonstrated for brittleness temperature versus phr of plasticizer and versus Shore hardness.

2.5 Volatility - weight loss after 24 hours at 130°C

The weight loss of 60phr 0.5mm pressed plaques in an oven with laminar airflow (17-21 air changes per hour) is listed below.

	DOP	Palatinol N	Hexamoll DINCH
Weight loss in %	3,93	1,19	2,42
Weight loss in mg/cm²	1,22	0,36	0,73

The volatility of specimens with Hexamoll DINCH is almost 50% below that of DOP and twice as high as with Palatinol N.

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2.6 Compatibility - "humidity compatibility" at 70°C / 100% r.h.

The humidity compatibility test (or environmental compatibility test) was run at 70°C and 100% relative humidity with 60phr pressed plaques. Samples were taken off the vapor chamber, wiped with a methanol soaked cloth and dried for 16 hours at 80°C. The reported change in weight in % is used to rank the compatibility of the plasticizer.

Storage time [days]	DOP	Palatinol N	Hexamoll DINCH
1	0,14	0,16	0,23
3	0,19	0,18	0,26
7	0,28	0,25	0,37
14	0,39	0,34	0,48
28	0,52	0,46	0,56

Within the accuracy of the test method the products showed comparable results with the tendency of slightly higher losses with Hexamoll DINCH. There was no sign of exudation on the surface of the specimens. No exudation and low weight loss indicate good compatibility even under severe environmental conditions such as high humidity at elevated temperatures.

2.7 Water extraction - resistance to extraction by water at 50°C

The 60 phr pressed plaques were immersed in demineralized water at 50°C. The water was changed weekly. Change in weight was measured both wet (remaining water was swabbed with paper towels) and dry (dried for 16 hours at 80°C in an oven).

Change in weight in % wet / dry

Immersion time [days]	DOP	Palatinol N	Hexamoll DINCH
1	+0,68 / -0,17	+0,68 / -0,18	+0,85 / -0,20
3	+0,90 / -0,24	+0,75 / -0,24	+1,09 / -0,27
7	+1,29 / -0,30	+1,20 / -0,27	+1,59 / -0,38
14	+1,54 / -0,41	+1,44 / -0,39	+1,78 / -0,48
28	+2,05 / -0,48	+2,01 / -0,48	+2,19 / -0,50

Comparable results were obtained with the three plasticizers. There was no sign of exudation on the surface of the specimens.

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2.8 Processing - dry blend time

The dry blend time was measured with a planetary mixer (attached to a Haake-Rheocord-System) at 95°C with Suspension PVC of K71.

	DOP	Palatinol N	Hexamoll DINCH
phr of plasticizer	60	63	68
Dry blend time	5 minutes 36 seconds	7 minutes 10 seconds	9 minutes 56 seconds
bulk density of the dry blend [g/cm³]	0,403	0,437	0,501

Without any friction in planetary mixers Hexamoll DINCH blends need longer to dry.
In high speed mixers, however, blending times might be shorter due to formulations and different levels of friction energy depending on process parameters and on the shape of rotor blades.

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3. Eco-toxicological profile of Hexamoll DINCH

The Safety of Hexamoll® DINCH

Hexamoll® DINCH has been thoroughly tested in order to ensure the safety of the product for its intended uses. The total cost for toxicological testing for DINCH is now over 5 million Euros. The studies, which followed the most recent OECD or EU guidelines, have clearly shown *no hazards* for the following endpoints: cancer, testicular toxicity, impairment of fertility, developmental toxicity, teratogenicity, and endocrine action.[1] *No environmental hazards* were observed, and the product does not accumulate in the body. In addition, DINCH is the only commercial plasticizer that has been shown to have *no adverse substance related effects* in developmental toxicity studies in rodent *and* non-rodent species.

The product has been assessed by the European Food Safety Authority (EFSA) for indirect food contact use[2] and the EU Scientific Committee on Emerging and Newly-Indentified Health Risks (SCENIHR) as an alternative plasticizer for the medical device market. [3] EFSA determined that *no specific migration limit* (SML) was required for DINCH. It is only limited by the default global migration limit, a generic limit for additives of 1 mg/kg food.

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1 Good summaries of these studies are publicly available in the EFSA and SCENIHR reviews referenced in this document.

2 The EFSA Journal (2006) 395 to 401, 1-21. Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food on a request related to a 12th list of substances for food contact materials. Adopted on 26 & 27 September 2006.

3 Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR). Opinion on the safety of medical devices containing DEHP-plasticized PVC or other plasticizers on neonates and other groups possibly at risk. 22nd Plenary, 6 February 2008.
http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_014.pdf

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File No: STD/1259

August 2008

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

1,2-Cyclohexanedicarboxylic acid, 1,2-diisononyl ester ('Hexamoll DINCH')

This Assessment has been compiled in accordance with the provisions of the *Industrial Chemicals (Notification and Assessment) Act 1989* (Cwlth) (the Act) and Regulations. This legislation is an Act of the Commonwealth of Australia. The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) is administered by the Department of Health and Ageing, and conducts the risk assessment for public health and occupational health and safety. The assessment of environmental risk is conducted by the Department of the Environment, Water, Heritage and the Arts.

For the purposes of subsection 78(1) of the Act, this Full Public Report may be inspected at our NICNAS office by appointment only at 334-336 Illawarra Road, Marrickville NSW 2204.

This Full Public Report is also available for viewing and downloading from the NICNAS website or available on request, free of charge, by contacting NICNAS. For requests and enquiries please contact the NICNAS Administration Coordinator at:

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Director
NICNAS

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FULL PUBLIC REPORT

1,2-Cyclohexanedicarboxylic acid, 1,2-diisononyl ester ('Hexamoll DINCH')

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
BASF Australia Ltd (ABN 62 008 437 867) of 500 Princes Highway, Noble Park VIC 3174

NOTIFICATION CATEGORY
Standard: Chemical other than polymer (more than 1 tonne per year).

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details claimed exempt from publication: Non-hazardous impurities, Import volume, Name and details of customers, and concentration of notified chemical in formulations.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
No variation to the schedule of data requirements is claimed.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
European Union (Identifier 99-04-1211), Canada (NDSL), in USA (TSCA), Japan, Korea and China.

2. IDENTITY OF CHEMICAL

CHEMICAL NAME
1,2-Cyclohexanedicarboxylic acid, 1,2-diisononyl ester

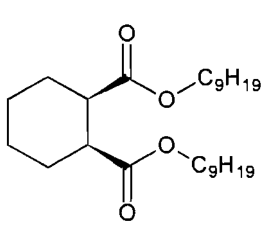
OTHER NAME(S)
1,2-Cyclohexanedicarboxylic acid, diisononyl ester (9CI)
1,2-Cyclohexanedicarboxylic acid, diisononyl ester, branched and linear
Diisononyl cyclohexane-1,2-dicarboxylate
DINCH

MARKETING NAME(S)
Hexamoll DINCH

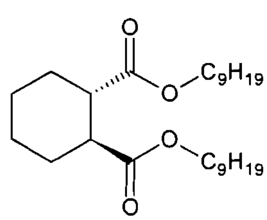
CAS NUMBER
166412-78-8

MOLECULAR FORMULA
$C_{26}H_{48}O_4$

STRUCTURAL FORMULA



90±10% *cis*- isomer



10±10% *trans*- isomer

MOLECULAR WEIGHT
424.6 g/mol

ANALYTICAL DATA
Reference ^{1}H-NMR, ^{13}C-NMR, IR, GC, and UV spectra were provided.

3. COMPOSITION

DEGREE OF PURITY
99.5%

HAZARDOUS IMPURITIES
None

NON-HAZARDOUS IMPURITIES
Several impurities (isomers and reaction by-products), each present at <0.5%.

ADDITIVES/ADJUVANTS
Formulations of the notified chemical may contain the following:

Chemical Name	Phenol, 4,4'-(1-methylethylidene)bis- ('Bisphenol A')		
CAS No.	80-05-7	*Weight %*	≤0.5%
Hazardous Properties	Conc ≥20%:	Xi; R36/37/38; R43	
	1% ≤ Conc <20%:	Xi; R43	

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20°C AND 101.3 kPa
Clear, colourless liquid. Appears homogeneous by visual inspection.

PROPERTY	VALUE	DATA SOURCE/JUSTIFICATION
Melting Point/Freezing Point	No freezing point. Glass transition <-90°C Pour point = -54°C	Did not crystallise Measured MSDS
Boiling Point	>351°C at 101.3 kPa 394°C	Decomposed before boiling at ~351°C Calculated
Density	947.2 kg/m^3 at 20°C	Measured
Viscosity	44-60 mPa.s at 20°C	Calculated
Vapour Pressure	2.2×10^{-8} kPa at 25°C 8.9×10^{-7} kPa at 50°C	Measured
Water Solubility*	<0.00002 g/L at 25°C	Measured
Hydrolysis as a Function of pH	Not determined	Insoluble in water
Partition Coefficient (n-octanol/water)	$\log P_{ow}$ = >6.2 at 25°C$\log P_{ow}$ = 10.0	MeasuredCalculated
Surface tension	30.7 mN/m at 20°C	Measured
Adsorption/Desorption	$\log K_{oc}$ >5.6 at 23°C $\log K_{oc}$ = 5.82	Measured Calculated
Dissociation Constant	Not determined	No modes of dissociation are expected
Particle Size	Not determined	The notified chemical is a liquid
Flash Point	224°C	MSDS
Flammability	Not highly flammable	Estimated
Autoignition Temperature	330°C	MSDS
Explosive Properties	Not explosive	Estimated

* *Note:* Additional solubility data is presented in Appendix A.

DISCUSSION OF PROPERTIES
The notified chemical is considered to be lipophilic, water-insoluble and surface-active. It is not expected to present a physical hazard; while combustible, it is not expected to present a flammable or explosive hazard. For full details of tests on physical and chemical properties, please refer to Appendix A.

Reactivity
The notified chemical is stable under the expected storage and use conditions, but is reported to react with strong oxidising agents. It is not expected to be oxidising of itself.

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will be imported in 200 L steel drums (majority), 1000 kg intermediate bulk containers (IBCs) or 20 tonne bulk isotainers.

MAXIMUM INTRODUCTION VOLUME OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	100-1000	100-1000	100-2000	100-2000	100-2000

PORT OF ENTRY
Victoria and NSW

IDENTITY OF MANUFACTURER/RECIPIENTS
BASF Australia Ltd. The notified chemical is expected to be used in plastics and other products by customers around Australia (primarily in Victoria and NSW).

TRANSPORTATION AND PACKAGING
The notified chemical will be distributed by road, by Orica Australia Limited.
Formulated products:

- Solid products, such as compound for formulation into flexible PVC, will be produced in the form of pellets and packaged in 25 kg bags or 500 kg bulky bins.
- Liquid products will be packaged in 200 L steel drums.

USE
The major applications for the notified chemical will use it as a plasticiser and impact modifier in food packaging, but also in general applications such as wire and cable, automotive, plastisols and other similar applications. The food contact applications can be grouped by the functions of the notified chemical, which are as a PVC plasticiser and as an impact modifier in polystyrene. The plasticiser is used in PVC cling films for fresh meat packaging, for aqueous food and fruits and vegetables, artificial corks, sealing gaskets for beverage containers, flexible tubes for beverages, alcoholic and non-alcoholic, conveyor belts for fatty and other foods, and as a polystyrene food packaging impact modifier.

OPERATION DESCRIPTION
The imported notified chemical will be formulated into PVC compound or plastisols, at up to 60% notified chemical content. In both cases, the notified chemical will be transferred to a weighing vessel and then pumped into a closed mixing vessel for blending with PVC and other additives such as stabilisers. Mixing will occur at elevated temperatures for dry blending (100-220°C) or at room temperature for plastisols. Dry blends will be compounded by extrusion and pelletised for packing into bags or bins. Plastisols, which vary from thin liquid dispersions to thick pastes, will be drummed off. The mixing vessels will be cleaned only when required. There may be clean downs required during routine or breakdown maintenance periods, where lines and vessels will be purged and cleaned with inert materials.

Compounded PVC will then be converted into end-use products by processes such as extrusion, calendering or injection moulding. For example, extrusion would be used for the production of flexible tubes for beverages, calendering for food cling film, sheeting and automotive upholstery, and injection moulding would be used for artificial wine corks.

Plastisols will be used for underbody coating, sealing, rotational coating, dipping, slush moulding, and spread coating (such as during the manufacture of tarpaulins). The plastisol liquid or paste may be poured into a mould, which will then be placed in an air-heated tunnel oven (130-160°C). Handling of the plastisol is typically automated, using vacuum pumps to transfer the plastisol directly into the mould.

6. HUMAN HEALTH IMPLICATIONS

6.1 Exposure assessment

6.1.1 Occupational exposure

NUMBER AND CATEGORY OF WORKERS

Category of Worker	*Number*	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport and storage			
Polymer stage	15	2	50
Product stage	15	1-2	40-50
Compounding and Manufacturing			
Reactor operation	50	12	20
Maintenance	20	1-2	240
QC testing	10	2	240
Transport & storage	10	2/4	240
End use	1000s	1-12	240

EXPOSURE DETAILS

Transport and storage

The notified chemical will be transported by road to a warehouse and then to the compounding facility. Exposure of receivers and transport personnel should only occur in the event of an accidental spillage.

Compounding

Incidental skin contact with the notified chemical may occur when the storemen insert the drum lance into the 200 L drum, or during connection of an IBC or isotank to the weighing vessel. Inhalation exposure to vapours may also occur during the transfer process. After mixing, intermittent skin contact may occur during the packaging process, from powdered blend or liquid plastisol. Quality control samples may also be taken at this stage, as technical personnel will make up small-scale compounds by hand in the laboratory.

During the subsequent compounding of dry blend into pellets, closed systems are used, and any exposure will be incidental. However, manual operations during this process may include opening of packages, connection/insertion of lines/hoses, pumping liquid products, and eventual removal of connections and closing the containers. In addition, maintenance workers may experience skin contact with the notified chemical.

For the specific formulation sites in Australia, approximately one third of the production time for the operators will be dedicated to running compound. During production runs (which can be up to 5 days long), the operators will work two 12-hour shifts, 5 days per week, and 48 weeks per year. Workers will prepare approximately 8 batches per day. Given the time that it takes to connect up and transfer product, the estimated period of direct contact with the notified chemical is less than 30 minutes per day for one person per shift.

Local exhaust ventilation will be employed at all workplace areas where natural ventilation is considered inadequate. Workers, particularly for those operators involved in any open transfer operations, wear personal protective equipment (PPE) including overalls, safety glasses/goggles and face splash shields, protective gloves, and are assumed to operate using appropriate industrial hygiene practices.

Product manufacture

Exposure to the notified chemical may occur during the processing of PVC compound or plastisol to manufacture the end-use product. Once compounded with PVC, the notified chemical is bound within the PVC matrix and exposure is unlikely. However, during product manufacture by processes such as extrusion, calendering and injection moulding, the elevated temperatures required may result in inhalation exposure to the notified chemical, whether from vapours or aerosols.

The methods for product manufacture from plastisols include spread coating, under-body coating, sealing, rotational coating, dipping and slush moulding. Although the processes are largely automated and enclosed, incidental skin contact with the notified chemical may occur during transfer of plastisol from drums to the moulding equipment. Workers are expected to wear PPE including overalls, gloves and eye protection.

End-use of products
Under normal circumstances, dermal exposure to the notified chemical is not expected during handling of PVC products, as it is expected to be physically bound within the PVC matrix. Exudation may occur during any heating of plastics, leading to possible skin and inhalation exposure to low levels of the notified chemical.

Occupational exposure estimation
For dermal exposure of workers involved in handling of the notified chemical during compounding and/or product manufacture, assuming non-dispersive use with some intermittent direct contact, EASE exposure modelling estimates the dermal exposure to the notified chemical to be 0-0.1 mg/cm^2/day (EC, 2003). However, the use of EASE for accurately predicting dermal exposures is thought to be limited in accuracy (EC, 2003). The RISKOFDERM project, based on measurements of industrial exposures, describes exposure levels to the hands for the addition of liquids into "large containers (or mixers) with large amounts (many litres) of liquids" (Marquart *et al*, 2006). In this study, a typical case exposure was described as 0.5 mg/cm^2/scenario, though a reasonable worst-case exposure was described as 14 mg/cm^2/scenario. Therefore, based on a reasonable exposure frequency of once daily and a whole-hand exposure (420 cm^2) to a 60 kg adult, a typical dermal exposure of 3.5 mg/kg bw/day is assumed. Worst-case, infrequent (whole-hand) exposures may be as high as 98 mg/kg bw/scenario.

Assuming a closed system with LEV, a highest-probable process temperature of 220°C (and excluding the possibility of aerosol formation), EASE estimates that the gas/vapour exposure to the notified chemical is likely to be 0-1.8 mg/m^3 (0-0.1 ppm) (EC, 2003). The same value is estimated for an identical system at 25°C. Therefore as a worst-case estimate, a 60 kg adult male worker exposed to vapours with an inhalation rate of 25.5 m^3/12-hour shift during medium activity (EC, 2003), might experience inhalation exposure to the notified chemical of 0-0.77 mg/kg bw/day.

Therefore, excluding oral exposure and assuming 10% dermal and 100% inhalation absorption (EC, 2003), the typical exposure during handling of the notified chemical is estimated to be 0.35-1.12 mg/kg bw/day.

6.1.2. Public exposure

The notified chemical in its imported form will only be available to industrial customers, and not to the general public. The public may be exposed to the notified chemical from its applications in products such as wire, cable and automotive parts, but the most significant public exposure is likely to occur through ingestion of the notified chemical following its migration from food packaging into food.

Migration into foods
The notified chemical has undergone assessment by the European Food Safety Authority in September 2006 (EFSA, 2006). For this assessment, the specific migration of the notified chemical was measured using various food simulants and representative foodstuffs, under different storage conditions. The specific migration of 10-17.8% notified chemical in plasticised PVC cling film into food simulants and foodstuffs was determined using a validated Gas Chromatography/Mass Spectrometry (GC/MS) method (Otter, 2007):

Test Sample	*Food*	*Extractable fat in food (%)*	*Migration conditions*	*Specific migration (mg/dm²)*
Cling film *(thickness 14 µm, 17.8% notified chemical)*	Sunflower oil	100	6-144 hours/ 10°C & 20°C	29 ± 2
	10% ethanol	0	24 hours/40°C	0.016 ± 0.002
	Turkey (escalope/Schnitzel)	1.0 ± 0.5	5 days/5°C	0.3 ± 0.1
	Pork (neck)	11.3 ± 2.5	5 days/5°C	1.2 ± 0.2
	Pork (escalope/Schnitzel)	0.7 ± 0.3	5 days/5°C	0.14 ± 0.01
		1.8 ± 0.3	5 days/5°C	0.30 ± 0.01
	Pork (liver)	5.0 ± 0.1	5 days/5°C	0.11 ± 0.02
	High fat cheese (nom. 60% fat)	44.3 ± 2.6	10 days/5°C	27.5 ± 2.2
	Low fat cheese (nom. 20% fat)	2.9 ± 1.0	10 days/5°C	2.4 ± 0.7
Cling Film *(thickness 14 µm, 12.2% not. chem.)*	Pork (neck)	14.7 ± 2.9	5 days/5°C	1.0 ± 0.3
	Pork (bacon)	22.1 ± 2.7	5 days/5°C	1.4 ± 0.1
Cling Film *(thickness 14 µm, 10% not. chem.)*	Pork (neck)	17.9 ± 0.5	5 days/5°C	0.5 ± 0.1
	Pork (bacon)	25.81 ± 2.4	5 days/5°C	0.8 ± 0.3

The notified chemical was found to migrate into foods with high fat content (e.g. ≤29 mg/dm^2 into sunflower oil, and ≤27.5 mg/dm^2 into high fat cheese). The migration of the notified chemical into food like fresh meat and low fat cheese was lower than that of foods containing higher fat levels (<2.4 mg/dm^2). The level of notified chemical in fresh meat at equilibrium was found to be proportional to the starting concentration in the cling film and relative to the fat content of the foods. In fatty foods, migration to equilibrium was achieved after 6 hours of

contact. Likewise, extraction studies from bottle closures using isooctane (in which the notified chemical is very soluble) show that it is able to extract an equilibrium concentration of the notified chemical after 5.3 hours.

For the use of the notified chemical in bottle sealing gaskets, artificial wine corks and beverage tubes, migration of the notified chemical into mineral water, grapefruit juice, soft drink or 15% ethanol was found to be very low (generally less than 0.11 mg/L, its solubility in 15% ethanol). This level of migration of the notified chemical is expected to apply for all aqueous foods (except alcoholic drinks with high ethanol content) as the low aqueous solubility of the notified chemical would limit its migration. Migration of the notified chemical from polystyrene (at the proposed use concentration) is expected to be lower than that from PVC. A test study using notified chemical-containing polystyrene sticks showed no migration of the notified chemical into olive oil or aqueous 10% ethanol (after 10 days at 40°C) above the detection limit of the analytical method (unpublished study provided by the notifier). Very low levels of migration of the notified chemical from polystyrene into aqueous 50% ethanol were observed.

For conveyor belts, migration into solid or semi-solid foods is expected to be limited by contact area and short contact times. Computer modelling of fatty food with ≤30 minutes contact time on a conveyor belt containing 12% notified chemical estimates specific migration rates of 12.4 mg/dm^2 at 20°C and 6.6 mg/dm^2 at 10°C (Otter, 2007). Therefore, assuming that migration into most foods will be considerably less than migration into oil, and that only the bottom of food is in contact with the conveyor belt (1 dm^2/kg), the migration of the notified chemical is expected to be <5 mg/kg food for ≤30 minutes contact time.

Dietary exposure estimation
On the request of NICNAS, Food Standards Australia New Zealand (FSANZ) has estimated the probable exposure of members of the Australian public to the notified chemical. This estimation was based on Australian food consumption data from the 1995 Australian National Nutrition Survey (NNS), which sampled the 24-hour food intake of 13,858 respondents aged 2 years and older (ABS, 1999). This is considered to be a representative sample of the Australian population and, as such, a diversity of food consumption patterns was reported. Mean consumption figures for all respondents were used to allow addition of potential dietary exposures across different foods.

Food consumption values for various food groups were combined with migration data to provide an estimate of potential dietary exposure to the notified chemical. The total exposure value thus derived provides a worst-case scenario of potential dietary exposure to the notified chemical because it is based on: (1) maximum migration rates, (2) mean food consumption values for broader groups of foods than there were migration data (in some cases) and (3) the highest migration rate where there were several for one food. Estimated dietary exposures were expressed per kilogram of body weight, based on the mean body weight for all respondents in the NNS survey aged 2 years and above, which was 67 kg for the Australian population.

Food	*% Fat content (fresh product)*	*Specific migration (mg/dm^2)*	*Migration (mg/kg)**	*Food Consumption (kg/day)*	*Public Exposure (mg/kg bw/day)*	*% Contri-bution*
All Oils[1]	100	29 ± 2	174	0.026 [1]	0.068	84
Ethanol 10%	0	0.016 ± 0.002	0.096	0	0.000	0
Turkey (escalope)	1 ± 0.5	0.3 ± 0.1	1.8	0.037 [2]	0.001	1
Pork	22.1 ± 2.7	1.4 ± 0.1	8.4	0.029 [3]	0.004	< 1
Pork (liver)	5 ± 0.1	0.1 ± 0.02	0.6	0.001[4]	0.000	0
High Fat Cheese	44.3	27.5 ± 2.2	165	0.002	0.005	6
Low Fat Cheese	11.4	2.4 ± 0.7	14.4	0.016	0.003	4
Total Exposure					0.081	

* A conversion factor of 6 is applied, based on a 1 L cube with 6×1 dm^2 surfaces (i.e. 6 dm^2/L) (Svensson, 2002).
1 Migration data based on sunflower oil, assumed true for all oils. Consumption value for all oils.
2 Consumption value for all poultry.
3 Consumption value for all pork meat and was assigned to the pork commodity with the highest migration data (bacon) to assume a worst-case scenario.
4 Consumption value for all mammalian offal.

The assumptions made in this dietary exposure estimation included:

- where a specific food was analysed, the notified chemical was assumed migrate equally into all products in that food group (e.g. sunflower oil to all oils), where no other data was available for other foods in the same food group.
- where migration data were assigned to a food classification, all foods in that group were considered to contain the notified chemical;

- all the foods within the group were considered to contain the notified chemical at the levels specified;
- unless otherwise specified, the maximum migration level in each food category has been used;
- food consumption from the 1995 NNS survey represents current Australian food consumption patterns;
- consumers always select products containing the notified chemical;
- 1 L of a food is equal to 1 kg;
- where there were no Australian or New Zealand data on the notified chemical's migration levels into a particular food group, it was assumed that overseas data were representative of these food groups; and
- where a food was not included in the dietary exposure assessment, it was assumed to contain a zero migration of the notified chemical.

Therefore, the worst-case dietary exposure to the notified chemical, based on Australian consumption levels, is estimated to be 0.081 mg/kg bw/day. The primary sources of dietary exposure to the notified chemical were oils (84%) and high fat cheese (6%). It should be noted that while the notified chemical might not be used to package oils directly, this worst-case exposure estimate should include migration of the notified chemical into other foods containing free oils (e.g. continental goods or dressed salads).

One weakness of this exposure estimation is the absence of dietary exposure to the notified chemical from meats other than pork. Consumption of beef by the Australian public is slightly higher than that of pork on a population basis, but that of lamb is less. Overall, this oversight is not expected to result in significantly inaccurate dietary exposure estimate, as pork consumption only accounts for <1% of total exposure to the notified chemical.

Dermal exposure
Members of the public are likely to make limited dermal contact with food packaging, wires, cables and/or automotive parts containing the notified chemical. Significant exposure to the notified chemical in plastic products as a result of casual contact during handling is not expected, as it is expected to be sufficiently bound within the plastic matrix. However, as the notified chemical will not be chemically bound, it may be released from products in low levels over time (e.g. volatilisation from car upholstery). The expected dermal exposure from prolonged contact with plastics containing the notified chemical cannot be accurately estimated, but may be significant as the notified chemical may partition from the plastic into the skin over time.

6.2. Human health effects assessment

The results from the toxicological investigations conducted on the notified chemical are summarised in the table below. The details of these studies can be found in Appendix B.

Endpoint and Result	*Assessment Conclusion*
Rat, acute oral	Low toxicity, LD_{50} >5000 mg/kg bw
Rat, acute dermal	Low toxicity, LD_{50} >2000 mg/kg bw
Rabbit, skin irritation	Slightly irritating
Rabbit, eye irritation	Not irritating
Guinea pig, skin sensitisation	No evidence of skin sensitisation
Rat, 28-day oral repeat dose toxicity	NOAEL 318 mg/kg bw/day (M), 342 mg/kg bw/day (F)
Rat, 90-day oral repeat dose toxicity	NOAEL 107.1 mg/kg bw/day (M), 389.4 mg/kg bw/day (F)
Rat, 2-year chronic toxicity/carcinogenicity	NOAEL 40 mg/kg bw/day (M), 200 mg/kg bw/day (F)
Rat, toxicokinetics and metabolism	Distribution to all organs and tissues was observed after rapid absorption. The oral bioavailability was calculated to be ~5-6% of a high dose and ~40-49% of a low dose, indicating saturation of gastrointestinal absorption. Accumulation was not observed in rats, and excretion was rapid, mainly via the faeces. Metabolism to several major metabolites: cyclohexanedicarboxylic acid (urine), monoisononyl cyclohexanedicarboxylate (faeces) & the glucuronide of monoisononyl cyclohexanedicarboxylate (bile).
Rat, liver enzyme induction	The notified chemical is an enzyme inductor of phase I and phase II liver enzymes in both male and female rats.
Rat, cell proliferation study	Increased cell proliferation was observed in the liver and the thyroid glands after 1 and 4 weeks of treatment, but after 13 weeks no increases in cell proliferation were observed.
Rat, thyroid function study	Indirectly toxic to the rat thyroid.
Bacterial reverse mutation assay	Non-mutagenic
In vitro chromosome aberration assay	Non-clastogenic
In vitro mammalian cell gene mutation test	Non-mutagenic

Endpoint and Result	*Assessment Conclusion*
In vivo mouse bone marrow micronucleus assay	Non-genotoxic
Rat, developmental toxicity	NOAEL 1200 mg/kg bw/day
Rabbit, developmental toxicity	NOAEL 1000 mg/kg bw/day
Rat, prenatal developmental toxicity	NOAEL 1000 mg/kg bw/day (for parental and F1 toxicity)
Rat, two-generation reproductive toxicity	NOAELs 1000 mg/kg bw/day (for parental and F2 toxicity), & 100 mg/kg bw/day (for F1 toxicity)

Toxicokinetics, metabolism and distribution
From the toxicology studies, the observed differences between oral administration (no systemic effects at 5000 mg/kg bw) and intraperitoneal injection (apathy, reduced spontaneity at 2000 mg/kg bw) immediately suggests that the notified chemical is either not readily absorbed following an oral dose, or that it undergoes extensive first-pass metabolism.

Poor oral absorption was supported in both the toxicokinetics and the metabolism studies, where oral absorption of the notified chemical saturated at higher doses, resulting in the majority of the notified chemical being recovered in faeces (84-100% for animals treated with 1000 mg/kg bw). The oral absorption that occurred was rapid (maximum after 1-2 hrs), but little indication of significant first pass metabolism was observed. The majority of faecal notified chemical was found to be excreted unchanged, and the level of metabolites in urine or bile represented only a small fraction of the administered dose.

None of the available data suggests that systemic absorption of the notified chemical can occur across the skin. Given its lipophilicity, the notified chemical may be taken up by the stratum corneum, but significant absorption it is not expected (EC, 2003).

Following gastrointestinal absorption, the notified chemical distributed to most bodily tissues within 1-8 hrs (highest levels were found in the gastrointestinal tract, adrenal glands, and liver; the lowest levels in brain, muscle, and bone), but it was not found to bioaccumulate. The plasma half-life of the notified chemical was found to be 4.4-11.9 hrs (depending on the administered dose), and its elimination exhibited biphasic kinetics. Excretion of the metabolites of any absorbed notified chemical was approximately equal into urine and bile.

The main metabolites of the notified chemical observed in metabolic studies in rats were the monoisononyl ester of cyclohexanedicarboxylic acid (eliminated through the bile) and cyclohexanedicarboxylic acid (eliminated in the urine). Glucuronide conjugates of the monoester of the notified chemical were observed in bile, and some evidence suggests that minor oxidative metabolites may undergo sulfate conjugation (from urine). While the notified chemical was found to be an inducer of metabolic liver enzymes (see below), its own excretion was unaffected after repeated doses.

Qualitatively, some similarities and some differences are observed between the metabolism, distribution and elimination patterns of the notified chemical and diisononyl phthalate (DINP) (NICNAS, 2007). The two chemicals are similar in structure, except that the notified chemical lacks the aromatic ring structure of DINP. Aromatisation of various derivatives of cyclohexanecarboxylic acid has been observed in liver from rat, guinea pig, rabbits and mice (Svardal and Scheline, 1985). This aromatisation activity was dependent on the presence of the carboxylic acid group, but 1,2-cyclohexanedicarboxylic acid (similar to the notified chemical) was unable to be aromatised. While this study used *trans*-cyclohexanedicarboxylic acid (c.f. predominantly *cis*- in the notified chemical), extrapolation from the results of the metabolism and toxicity studies provided by the notifier support similar conclusions for the notified chemical—i.e. no phthalates were observed in the metabolism study. The notified chemical is not expected to be able to aromatise to form DINP (or its metabolites) *in vivo*.

Acute toxicity
The notified chemical is not expected to be acutely toxic by any route of administration. No significant effects were observed after single large doses in the acute oral and dermal toxicity studies, and only minor systemic effects were observed after intraperitoneal injection in the *in vivo* micronucleus study.

Irritation and Sensitisation
The notified chemical is expected to be at most a weak skin irritant. It does not contain any known structural alerts for skin irritation potential, other than its surface-activity (Hulzebos *et al*, 2005). Moderate erythema was observed up to 72 hours in the acute dermal irritation study, and mild erythema was also observed in the acute dermal toxicity study. These results were not, however, of sufficient severity for the classification of the notified chemical. Only minimal irritation was observed in the eye irritation study.

The notified chemical contains no structural alerts for sensitisation (Barratt *et al*, 1994), was negative in a guinea pig maximisation study, and is therefore not considered to be a skin sensitiser.

Repeated Dose Toxicity

Liver effects and enzyme induction

Treatment of test animals with the notified chemical was found to result in increases in liver weights in the 90-day and 2-year repeated dose studies, in the cell proliferation study, and in the 2-generation study. Other signs of liver effects in these studies included elevations of serum γ-glutamyltransferase activity and decreased serum bilirubin concentrations. No histopathological evidence of liver toxicity was observed.

This spectrum of treatment-related effects is known to result from hepatic enzyme induction. To show that the notified chemical was able to induce liver enzymes, two special studies were carried out. These studies showed that (1) the notified chemical is an inducer of both phase I and phase II enzymes in the liver, and (2) that treatment of rats with the notified chemical induces cell proliferation in the liver that accounts for the increased organ weights observed.

Therefore, any observed effects that are thought to result from liver enzyme induction are interpreted to be adaptive metabolic changes, and not pathological changes.

Thyroid effects

The 2-year combined chronic toxicity/carcinogenicity study with the notified chemical revealed effects on the thyroid as the most significant adverse effect. The key findings were increased absolute and relative thyroid weight, altered thyroid colloid, and an increase incidence of thyroid follicular cell adenomas at 24 months. Thyroid follicular cell proliferation and changes in TSH levels were also observed at comparable dose levels in the 90-day rat study, in a 13 week cell proliferation study, and also in female rats in the 2-generation reproduction toxicity study.

The notifier has argued that these thyroid effects are not significant for human health risk assessment because of differences between rats and humans in thyroid hormone handling and sensitivity to thyroid-disturbing mechanisms. This conclusion is reasonable, and consistent with EFSA and IARC opinion on the significance of thyroid follicular cell tumours induced by chemicals which alter thyroid hormone metabolism and which demonstrate a lack of genotoxic potential (IARC, 1999; Rice *et al*, 1999; EFSA, 2006). It is reasonably well established that in the rat, thyroid follicular-cell tumours are commonly associated with imbalances in TSH levels resulting in sustained stimulation of the thyroid gland by TSH feed-back stimulation of the hypothalamic-pituitary-thyroid axis, leading to secondary hyperplastic or neoplastic changes with thyroid adenoma or carcinoma formation. The human thyroid gland is much less susceptible to this pathological phenomenon than rodents (Capen, 1997). Even in patients with markedly altered changes in thyroid function and elevated TSH levels, there is little if any increase in the incidence of thyroid cancer (Curran and DeGroot, 1991; Capen, 1997). The increased sensitivity of the rodent thyroid gland to perturbations by drugs and chemicals is related to the shorter plasma half-life of thyroxine (T4) in rodents (12-24 h) when compared to humans (5-9 days), due to the considerable differences in the transport proteins for thyroid hormones between species (Capen, 1997). In humans, serum T4 is bound primarily to thyroxine-binding globulin, a protein that is not present in rodents.

The proposal that thyroid effects of the notified chemical in rats are associated with an indirect mechanism was supported by the performance of special mechanistic studies. These demonstrated that, at relevant dose rates in rats, hepatic metabolic pathways involved in T4 conjugation are strongly induced, and that T3, T4 and FSH levels are perturbed in a manner consistent with an indirectly acting enzyme inducer (phenobarbital). The effects observed were not comparable to those associated with a direct inhibitor of iodine incorporation into thyroid hormones (propylthiouracil). The effects of the notified chemical on thyroid hormone metabolism are also not unlike those of polyhalogenated biphenyls, which increase the glucuronidation of T4 and increase TSH, and thyroid uptake of iodine in rats, but less so in mice (Capen, 1997; Craft *et al*, 2002). What is not known (although it appears to be unlikely for the notified chemical), is whether hydroxylated metabolites can have a direct effect on thyroid hormone receptor-activated gene expression, as has been suggested for PCB metabolites (Kimura-Kuroda *et al*, 2007).

A dose-dependent increase in the incidence of altered thyroid follicular colloid (described as "flaky") was observed in female animals in the 2-year study (at 12 months), in male rats after 13 weeks in the cell proliferation study, and in female F1 rats in the 2-generation study (<1 year at terminal sacrifice). In another rat strain, Sprague-Dawley, changes in follicular colloid have been reported as a normal effect of ageing, beginning at 56 weeks of age (Rao-Rupanagudi *et al*, 1992). The increased incidence of flaky colloid observed in the 2-year study in both control and notified chemical-treated rats would be consistent with this mechanism after 24 months. However, an increased incidence of this effect in notified chemical-treated animals of ≤1 year in age (absent in control and low-dose animals) was reported in several studies. This effect is not known to be caused by liver enzyme induction. Therefore, as the nature and/or pathogenesis of the effect are not known, it cannot be considered as non-adverse. Altered colloid was observed at 300 mg/kg bw/day (F1 females) in the 2-generation study (NOAEL of 100 mg/kg bw/day).

Kidney effects
The kidney is a probable target organ for the toxicity of the notified chemical. Treatment-related increases in kidney weights were predominantly observed in male rats in the 90-day and 2-year repeated dose studies, in the cell proliferation study, and in the 2-generation study. While these increases correlate with the observation of male-only kidney cortical cell proliferation in the S-phase response study (although this finding was of questionable significance), increased kidney weights were also observed in female rats in the 90-day and 2-generation studies. No data was available regarding the reversibility of kidney weight changes.

Microscopically, deposition of α2μ-microglobulin was observed in the proximal tubules of the renal cortex in all treated males in the 90-day study, but not in the 2-year study. However, α2μ-microglobulin deposition is a rat-specific effect without relevance to the determination of human hazard. The treatment-related vacuolisation of the tubular epithelia of male F1 animals in the two-generation study is considered a relevant effect of treatment with the notified chemical, although what it may indicate is uncertain.

Degenerated epithelial cells were found in the urine of male rats in the 28- and 90-day studies. The notifier's toxicology laboratory reports that these effects are a transient effect in younger animals of the strain used, and has been observed following treatment with several structurally unrelated chemicals. This claim is supported by the fact that these effects were not observed in the 2-year study, or in animals over 20 weeks of age in the 2-generation study. However, in both the 28-day and the 90-day studies, these findings were reported as treatment-related adverse effects, and no data has subsequently made available to support this claim. In the 90-day study, mid- and high-dose animals also showed increased blood cells in urine at one measurement interval.

Increases in kidney weight may be a result of the notified chemical's ability to induce phase I and phase II metabolic enzymes in the kidney. However, such enzyme induction has only been demonstrated for the notified chemical in the liver, and xenobiotic treatment that induces liver metabolism may not induce induction of enzymes in the kidney (e.g. phenobarbital (Khan and Alden, 2002)). Similarly, cell proliferation resulting from treatment with the notified chemical has only been observed in males, yet increases in kidney weight were also observed in females. Therefore, in the absence of data on the notified chemical's ability to induce kidney metabolism, increases in kidney weight as a response to the notified chemical cannot be considered to be of no toxicological relevance.

Kidney effects were observed with an NOAEL of 40 mg/kg bw/day in the 2-year study and 100 mg/kg bw/day in the 2-generation study.

Lack of proliferative effects on peroxisomes
No peroxisome proliferative effects related to activation of the PPARα receptor were observed for the notified chemical (c.f. phthalate esters like DINP). No effects were observed on cyanide-insensitive palmitoyl CoA oxidase in the 90-day study, and no peroxisome accumulation was observed in any of the repeat dose oral toxicity studies. Also unlike DINP, the notified chemical caused no increase in the incidence of hepatic or pancreatic acinar cell tumours, nor did it appear to cause testicular degeneration (NICNAS, 2007).

Toxicity for Reproduction and Development
In four separate studies on the toxicity of the notified chemical on reproduction and development, no effects were observed on mating, male or female fertility, fecundity or gestational parameters, and it was found to be not teratogenic. All observed effects were restricted to general toxicity. The kidney effects observed only in the F1 generation (described above) were noteworthy.

No significant treatment-related effects on anogenital distance were observed in any of the reproductive toxicity studies, suggesting that the notified chemical does not possess endocrine disrupting effects of the kind seen with phthalate esters, e.g. the antiandrogenic effects observed for dibutyl phthalate (Mylchreest *et al*, 1998).

Genotoxicity
The notified chemical was found to be non-genotoxic in three different *in vitro* studies. In addition, an *in vivo* mouse bone marrow micronucleus study gave a non-genotoxic result (although no cytotoxicity to the target tissue was observed, the notified chemical's distribution to the bone marrow was demonstrated in the toxicokinetics study). Overall, there were no genotoxic effects observed in any test using the notified chemical.

Carcinogenicity
An increased number of thyroid follicular adenomas were observed in the 2-year rat study, and this was proposed by the notifier to occur as a result of an increase in thyroid hormone (T3 and T4) metabolism due to liver enzyme induction by the notified chemical, (as described above). Based on the recommendations of the IARC, the absence of any genotoxic activity indicates that the thyroid follicular adenomas observed are a secondary effect to liver enzyme induction in the rat (IARC, 1999). Thus, these tumours are not considered relevant to human health risk assessment.

After 2 years of treatment, an increase in the number of fibroadenomas was observed in the mammary glands of high dose females. However, the significance of this increase may be discounted because the incidence was only marginally higher than historical data in this strain of rats, and there was no increased incidence of malignancies (adenocarcinomas). The incidence of this tumour in the control group was low in relation to these historical data.

No Observed Adverse effect Level (NOAEL)
The NOAEL of the notified chemical (after oral administration) is considered to be 40 mg/kg bw/day, based on the lowest tested dose (from the 2-year study) where an absence of significant kidney effects was observed.

Hazard Classification
Based on the available data the notified chemical is not classified as hazardous under the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

6.3. Human health risk characterisation

6.3.1. Occupational health and safety

Transport and storage workers should only be exposed to the notified chemical in the event of an accidental spillage, and so are unlikely to experience any risk from the notified chemical.

Predominantly incidental dermal exposure can be expected during compounding of plastisols or during the manufacture of plastic products (given the types of duties carried out). The main compounding processes (e.g. dry blending) are expected to be largely automated and enclosed, so incidental inhalation exposures to vapours resulting from high process temperatures are probable.

The estimated typical exposure to the notified chemical during compounding and/or product manufacture is estimated to be 0.35-1.12 mg/kg bw/day (for all routes of exposure). Considering the lowest NOAEL of the notified chemical, 40 mg/kg bw/day, a Margin of Exposure (MOE) range of 35.9-114 is calculated. These MOE values indicate that additional exposure control measures may be necessary during long-term, repeated handling of the notified chemical or during activities around high temperature areas where it will be processed.

Single-event dermal exposures of up to 98 mg/kg bw/scenario are possible. However, the notified chemical is of low acute dermal toxicity (LD_{50} >2000 mg/kg bw) and so such exposure is unlikely to present an acute health risk. However, given that the notified chemical has slight skin irritant characteristics, the wearing of protective equipment would be recommended to prevent against such exposures.

The notifier has described the exposure control measures that are proposed at sites where the notified chemical is handled. These include:

- Adequate exhaust ventilation is expected to be applied during high temperature processes, as vapours of varying hazard are expected in these applications. Thorough ventilation is recommended at all sites where the notified chemical is handled.
- Worker PPE (including overalls, safety glasses, and protective gloves) is expected to be adequate to minimise most foreseeable dermal and ocular exposure.

Exposure to finished plastic articles containing the notified chemical is not expected to result in significant exposure to the notified chemical, and therefore any risk to workers handling these articles is expected to be commensurately negligible.

Given the notified chemical's non-hazardous nature, and the reported handling conditions, it is not considered to pose an unacceptable risk to occupational health and safety.

6.3.2. Public health

Significant migration of the notified chemical is expected into packaged high-fat foods (≥20% fat content) with PVC cling films and other food packaging. These foods form part of the normal Australian diet, and therefore daily exposure to the notified chemical would be expected to a significant proportion of the population. Based on the available data, a significant proportion of any ingested notified chemical is likely to be systemically absorbed.

In order to estimate the risk associated with this ingestion, a comparison of the toxicological data with the worst-case exposure estimate gives:

NOAEL for kidney effects in rats	=	40 mg/kg bw/day
Safety factor (for extrapolation from animal data)	=	100
Tolerable Daily Intake (TDI)	=	0.40 mg/kg bw/day
Estimated worst-case, long-term dietary exposure	=	0.081 mg/kg bw/day
Estimated exposure as a percentage of TDI	=	20.3%

Therefore, despite numerous conservative assumptions (both in the exposure estimation and in the use of a safety factor from a NOAEL), the expected worst-case public exposure is considered to be acceptable – much lower than a level that might be expected to produce adverse effects. Even accounting for any apparent weaknesses in the exposure estimation, the TDI is unlikely to be exceeded. In addition, as the exposure estimation was well below the TDI, the 'worst-case' dietary exposure estimation was not considered to require further refinement.

Dermal exposure to plastics containing the notified chemical is expected to be low, due to it being incorporated within the plastic matrix. Combined with the low dermal toxicity and low irritant and sensitisation potential of the notified chemical, dermal exposure of the public is unlikely to pose any significant risk to public health, even after prolonged exposure.

In conclusion, the notified chemical is not considered to pose a significant risk to public health at the levels of exposure that are estimated to result from its proposed use.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1 Environmental Exposure

RELEASE OF CHEMICAL AT SITE
Import and Transport
Release of the notified chemical to the environment during importation and transport of the notified chemical is expected to be minimal, unless exposure occurs as a result of accidental spillage.

The notifier estimates that at the maximum import volume, less than 1000 kg of the notified chemical would remain in the import containers. This will be either disposed of to landfill, with the bladders from flexitainers or drums, or as rinsings from isotainers and drums by waste disposal contractors.

Addition of Stabiliser
In some instances a stabiliser may need to be added to the imported product. This will be achieved by pumping the contents of an imported isotainer into a mixing vessel, adding the stabiliser, mixing and returning the product to the isotainer. The mixing vessel will be rinsed and the rinsate disposed of to the sewer. Assuming 30% of the import volume is stabilised, ~210 kg of notified chemical will be disposed of to the sewer with the rinsate.

PVC Compounding
There are two main methods of compounding for processing of PVC, dryblending and plastisol blending. Losses for these methods are described below. In addition to these sources of release, residues in containers may be released. Empty drums will be triple rinsed with washings processed to EPA regulations. IBCs and isotainers are expected to be reused.

- Dryblending will be conducted in lidded vessels. The method will be based on suspension or mass grade PVC and typically consists of mixing all ingredients with a high-speed rotating agitator that heats the material by friction. Temperatures of 100-200°C are reached and the liquid plasticiser will be completely adsorbed by the fine PVC powder grain. Residence times in the lidded blender will be of the order of 15 minutes, after which the hot blend will be dropped into a cooling blender for rapid cooling to avoid lumping. During this process the exposure of the hot material to open air will be small. Assuming one air exchange per run, the amount of emitted plasticiser is claimed to be 0.0037%. It is anticipated that these emissions would largely be trapped by local exhaust ventilations systems.
- Plastisol blending will take place in stirred vessels at ambient temperature. To avoid the development of high viscosities by swelling of the PVC particles due to plasticiser uptake, the vessels have to be cooled to remove the heat of friction. Any significant emission of plasticisers at ambient temperature is excluded (emission = 0%).

PVC Product Manufacture
An estimated 0.035% per annum of the import volume of notified chemical would be released into the environment due to the manufacture of PVC products. This release would primarily result from volatilisation during processing into finished articles.

Periodically, extrusion equipment will be cleared of off-grade polymer by a purging process. This purging process will account for approximately 0.4% of the waste notified chemical. The purged material would be recycled or collected and buried in an approved landfill as general waste.

RELEASE OF CHEMICAL FROM USE
Some recycling of PVC products will occur at specialised PVC recyclers (e.g. Cryogrind, Nylex SRM). Ultimately, however, the majority of the objects containing the notified chemical will be disposed of to landfill at the end of their useful life. As the notified chemical is not bound within the PVC matrix, it will be lost from PVC articles containing it. This release may occur through blooming followed by volatilisation or leaching.

RELEASE OF CHEMICAL FROM DISPOSAL
The recommended method of disposal of liquid wastes containing materials such as the notified chemical is by burning in an approved incinerator.

7.1.2 Environmental fate

Endpoint	*Result*	*Assessment Conclusion*
Ready biodegradability	41% in 28 days	Not readily biodegradable
Bioaccumulation	30-day BCF = 189.3 (14-day exposure + 16 day depuration)	Not likely to bioaccumulate

For the details of the environmental fate studies please refer to Appendix C'.

7.1.3 Predicted Environmental Concentration (PEC)

The majority of the notified chemical will be incorporated into impact modified food packaging (85%) and in general applications such as wire and cable, automotive, plastisols and other similar applications. During the lifetime of the articles, the notified chemical may be released from the article either through blooming (movement to the surface of the plastic) followed by evaporation or through leaching.

Wastes generated during compounding with PVC or manufacture of plastic articles will enter either landfill or the sewage system. Simpletreat modelling of the notified chemical indicates that 26% will be released to air, 3% to water, 68% to sludge and 1% degraded resulting in 69% removal during passage through a sewage treatment plant (EU, 2001).

The half-life in air through reaction with hydroxide radicals is determined using the AOP program produced by Syracuse Corporation. The following values were generated using the EPIWIN modelling on the notified chemical:

Compartment	Half-life
Air	8.35 hours
Surface water	360 days
Soil/aerobic sediment	720 days
Anaerobic sediment	3240 days

It is anticipated that the notified chemical would display similar half-lives in each of the environmental compartments, and potentially be persistent in some soils and sediments due to it being not readily biodegradable.

7.2. Environmental effects assessment

The results from ecotoxicological investigations conducted on the notified chemical are summarised in the table below. The details of these studies can be found in Appendix C.

Endpoint	*Result*	*Assessment Conclusion*
Fish toxicity*	96-hour LC_{50} >100 mg/L	Not toxic to fish
Daphnia Toxicity (acute)	48 h LC_{50} >100 mg/L WAF**	Not toxic to *Daphnia*
Daphnia Toxicity (chronic)	21-day NOEC = 0.021 mg/L	Not toxic to *Daphnia*
Algal Toxicity	72-hour E_rC_{50} >100 mg/L WAF** 72-hour E_bC_{50} >100 mg/L WAF**	Not toxic to algae
Inhibition of Bacterial Respiration	180 min EC_{50} >1000 mg/L	Low toxicity to bacteria
Earthworm Toxicity	14-day LC_{50} >1000 mg/kg	Not toxic to earthworms
Emergence and growth of higher plants	20/21-day EC_{50} >1000 mg/kg	Not toxic to higher plants

* Nominal concentration contained considerable undissolved substance.
** The amount of notified chemical present in solution was not determined.

7.2.1 Predicted No-Effect Concentration

Based on the ecotoxicity data provided, the notified chemical is not toxic up to the limit of water solubility. Therefore, a PNEC could not be calculated.

7.3. Environmental risk assessment

The major applications for the notified chemical will be as a plasticiser and impact modifier in food packaging (85%) and in general applications such as wire and cable, automotive, plastisols and other similar applications (15%). The maximum process temperature during the manufacture of food-contact materials containing the notified chemical is ~220°C, well below the thermal decomposition temperature of ~351°C. Therefore, no thermal decomposition is expected under usual processing conditions. The notified chemical may also be used in traditional use functions. These include as a plasticiser for polyvinyl chloride (PVC) and vinyl chloride copolymers. The end use products containing the notified chemical include automobile undercoating, building materials, wires, cables, shoes, carpet backing, pool liners and gloves.

Once the chemical has been incorporated in plastic articles the majority of the notified chemical is expected to remain within the plastic matrices. Hence, the majority of the notified chemical will share the fate of the articles into which it is incorporated. It is anticipated that these will be disposed of to landfill at the end of their useful lifetime. The notified chemical is not expected to leach from landfill. There may also be some recycling.

The recommended method of disposal of wastes containing the notified chemical is incineration. Any incineration of the notified chemical will result in the formation of water vapour and oxides of carbon.

Some blooming and subsequent evaporation or leaching of the notified chemical may be anticipated during the useful lifetime of the articles into which it has been incorporated. These releases are expected to be dispersed in nature and at low levels. Any material partitioning to the air through evaporation would also rapidly degrade through reaction with hydroxyl radicals.

The above considerations indicate acceptable risk to the environment when the notified chemical is used in the manner and levels indicated by the notifier.

8. CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification

Based on the available data the notified chemical is not classified as hazardous under the NOHSC *Approved Criteria for Classifying Hazardous Substances*.

and

In addition, the notified chemical is not classified using the Globally Harmonised System for the Classification and Labelling of Chemicals (GHS) (United Nations 2003). This system is not mandated in Australia and carries no legal status but is presented for information purposes.

Human health risk assessment

Under the conditions of the occupational settings described, the notified chemical is not considered to pose an unacceptable risk to workers.

When used in the proposed manner, the notified chemical is not considered to pose an unacceptable risk to public health.

Environmental risk assessment

The chemical is not considered to pose a risk to the environment based on its reported use pattern.

Recommendations

CONTROL MEASURES

Occupational Health and Safety

- Employers should implement the following engineering controls to minimise occupational exposure to the notified chemical where the liquid imported product and/or formulated products containing it are handled during mixing and blending operations:
  - *Ensure adequate local ventilation*

- Employers should implement the following safe work practices to minimise occupational exposure during the handling of the notified chemical as introduced and in liquid formulations:
  - *Avoid direct skin contact*

- Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical as introduced and in liquid formulations:
  - *Gloves, safety glasses and coveralls*

  Guidance in selection of personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

- A copy of the MSDS should be easily accessible to employees.

- If products and mixtures containing the notified chemical are classified as hazardous to health in accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances*, workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation must be in operation.

Environment

- Do not empty the notified chemical into drains.

Disposal

- The notified chemical should be disposed of by incineration or landfill in accordance with the local regulations.

- Packaging that is contaminated with the notified chemical should be emptied, thoroughly cleaned and recycled.

Emergency procedures

- Pick up spilled material with suitable absorbent material. Dispose of absorbed material in accordance with local regulations.

Regulatory Obligations

Secondary Notification

This risk assessment is based on the information available at the time of notification. The Director may call for the reassessment of the chemical under secondary notification provisions based on changes in certain circumstances. Under Section 64 of the *Industrial Chemicals (Notification and Assessment) Act (1989)* the notifier, as well as any other importer or manufacturer of the notified chemical, have post-assessment regulatory obligations to notify NICNAS when any of these circumstances change. These obligations apply even when the notified chemical is listed on the Australian Inventory of Chemical Substances (AICS).

Therefore, the Director of Chemicals Notification and Assessment must be notified in writing within 28 days by the notifier, other importer or manufacturer:

(1) Under Section 64(2) of the Act; if
  - the function or use of the chemical has changed from a plasticiser or impact modifier for PVC or polystyrene, or is likely to change significantly;

- the amount of chemical being introduced has increased from 2000 tonnes, or is likely to increase, significantly;
- if the chemical has begun to be manufactured in Australia;
- additional information has become available to the person as to an adverse effect of the chemical on occupational health and safety, public health, or the environment.

The Director will then decide whether a reassessment (i.e. a secondary notification and assessment) is required.

No additional secondary notification conditions are stipulated.

Material Safety Data Sheet
The MSDS of the notified chemical provided by the notifier was reviewed by NICNAS. The accuracy of the information on the MSDS remains the responsibility of the applicant.

APPENDIX A: PHYSICO-CHEMICAL PROPERTIES

Melting Point/Freezing Point
No melting point.
Glass transition temperature = <-90°C
Pour point = -54°C

METHOD	OECD TG 102 Melting Point/Melting Range.
Remarks	Test was not conducted, as the test substance could not be prompted to crystallise. A glass transition occurred at slightly below -90°C.
TEST FACILITY	BASF (1999a)

Boiling Point
>351°C at 101.3 kPa
394°C (calculated)

METHOD	EC Directive 92/69/EEC A.2 Boiling Temperature.
Remarks	The notified chemical decomposed before boiling at ~351°C (determined by differential scanning calorimetry). The boiling point was obtained via extrapolation.
TEST FACILITY	BASF (1999a)

Density
947.2 kg/m^3 at 20°C

METHOD	OECD TG 109 Density of Liquids and Solids.
Remarks	Determined using the pycnometer method.
TEST FACILITY	BASF (1999a)

Viscosity
44-60 mPa.s at 20°C

METHOD	German Standard method DIN 51562/D 445
Remarks	Determined by calculation from the measured kinematic viscosity. Further details of experiment are not known.
DATA SOURCE	BASF Technical data sheet "Hexamoll DINCH"

Vapour Pressure
2.2×10^{-8} kPa at 25°C
8.9×10^{-7} kPa at 50°C

METHOD	EC Directive 92/69/EEC A.4 Vapour Pressure.
Remarks	The vapour pressure was determined by extrapolation from measurements at 43.6°C to 118.2°C. No details of how these were derived are available. The substance is very slightly volatile (Mensink *et al*, 1995).
TEST FACILITY	BASF (1999a)

Water Solubility
<0.00002 g/L at 25°C

METHOD	EC Directive 92/69/EEC A.6 Water Solubility.
Remarks	Column Elution Method. Quantitative analysis was by gas chromatography.
TEST FACILITY	BASF (1999a)

Solubility in other systems
≤0.0001 g/L (in 3% aqueous acetic acid)
0.00011 ± 0.00004 g/L (in 15% ethanol in water)
Soluble in tetrahydrofuran (THF), ethyl acetate, methyl ethyl ketone, toluene, acetone, and dimethylsulfoxide (DMSO)

Remarks	Methods unspecified. Measurements carried out at room temperature.
REFERENCE	Otter (2007)

Partition Coefficient (*n*-octanol/water)	$\log P_{ow}$ = >6.2 at 25°C$\log P_{ow}$ = 10.0 (calculated)
METHOD	EC Directive 92/69/EEC A.8 Partition Coefficient.
Remarks	HPLC Method. The retention of the notified chemical on the reverse-phase column was greater than that of DDT ($\log P_{ow}$ = 6.2). Calculated using KVVWIN v1.51.
TEST FACILITY	BASF (1999a)

Surface Tension	30.7 mN/m at 20°C
METHOD	German standard method DIN EN 14370
Remarks	Details of experiment are not known. The notified chemical is considered to be surface active based on this result.
DATA SOURCE	BASF Technical data sheet "Hexamoll DINCH"

Adsorption/Desorption	Log K_{oc} > 5.6 at 23°C (measured) $\log K_{oc}$ = 5.82 (calculated)
METHOD	OECD TG 121 Estimation of the Adsorption Coefficient (K) on soil and sewage sludge using High Performance Liquid Chromatography (HPLC).
Remarks	As the retention time of the test substance was higher than that of reference substance (DDT) the value of log K_{oc} of the test substance was estimated as > 5.6.
TEST FACILITY	BASF (2002a)

Flash Point	224°C
METHOD	German standard method DIN ISO 3016
Remarks	Details of experiment are not known.
DATA SOURCE	BASF MSDS "Hexamoll DINCH"

Flammability	Not highly flammable
Remarks	Not expected to be highly flammable, based on its physicochemical properties and experience in use.

Autoignition Temperature	330°C
METHOD	German standard method DIN 51794
Remarks	Details of experiment are not known.
DATA SOURCE	BASF MSDS "Hexamoll DINCH"

Explosive Properties	Not explosive
Remarks	The notified chemical is predicted to be not explosive based on its physicochemical properties and structural considerations.

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE Notified chemical (99.7% pure)

METHOD OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method.
EC Directive 96/54/EC B.1.tris: Acute Toxicity (Oral)
EPA / OPPTS Guideline 870.1100 Acute Oral Toxicity

Species/Strain Rat/Wistar chbb:thorn
Vehicle Olive Oil
Remarks – Method Initially, 5000 mg/kg bw was administered to three males. Due to the absence of mortality, the same dose was then given to three females .

RESULTS

Dose (mg/kg bw)	*Number and Sex of Animals*	*Mortality*
5000	3 per sex	0/6

LD_{50} >5000 mg/kg bw
Signs of Toxicity No signs of systemic toxicity were observed, and the expected weight gain was observed during the observation period.
Effects in Organs No abnormalities were found at necropsy of animals sacrificed at the end of the study.
Remarks – Results None.

CONCLUSION The notified chemical is of low toxicity via the oral route.

TEST FACILITY BASF (1999c)

B.2. Acute toxicity – dermal

TEST SUBSTANCE Notified chemical (99.7% pure).

METHOD OECD TG 402 Acute Dermal Toxicity.
EC Directive 92/69/EEC B.3 Acute Toxicity (Dermal)
EPA / OPPTS Guideline 870.1200

Species/Strain Rat/Wistar chbb:thorn
Vehicle None (administered undiluted)
Type of dressing Semi-occlusive
Remarks – Method No significant protocol deviations.

RESULTS

Dose (mg/kg bw)	*Number and Sex of Animals*	*Mortality*
2000	5 per sex	0/10

LD_{50} >2000 mg/kg bw
Signs of Toxicity - Local Very slight erythema or well-defined erythema was observed in all female and male animals, after removal of the dressing.
Signs of Toxicity - Systemic No signs of toxicity were observed, and the expected weight gain was observed during the observation period.
Effects in Organs No abnormalities were noted at necropsy of animals sacrificed at the end of the study.
Remarks – Results None

CONCLUSION The notified chemical is of low toxicity via the dermal route.

TEST FACILITY BASF (1999d)

B.3. Irritation – skin

TEST SUBSTANCE: Notified chemical (99.94% pure)

METHOD: OECD TG 404 Acute Dermal Irritation/Corrosion.
EC Directive 92/69/EEC B.4 Acute Toxicity (Skin Irritation)
US EPA OPPTS 870.2500 Acute Dermal Irritation

- Species/Strain: Rabbit/New Zealand White A1077 INRA
- Number of Animals: 1 male, 2 female
- Vehicle: None (0.5 mL liquid test substance applied undiluted)
- Observation Period: 14 days
- Type of Dressing: Semi-occlusive.
- Remarks – Method: No significant protocol deviations.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Erythema/Eschar	1.7	1.7	2.0	2	7 days	0
Oedema	0	0	0	0	0	0

*Calculated on the basis of the scores at 24, 48, and 72 hours for EACH animal.

Remarks – Results: Moderate erythema was observed in all animals immediately after removal of the patch and this persisted in two animals up to the 48-hour observation. Slight to mild erythema were observed in all animals at the 72-hour observation. These effects were reversible in two animals within 7 days of removal of the patch, and in the third animal within 14 days.

CONCLUSION: The notified chemical is slightly irritating to skin.

TEST FACILITY: BASF (2004a)

B.4. Irritation – eye

TEST SUBSTANCE: Notified chemical (99.7% pure)

METHOD: OECD TG 405 Acute Eye Irritation/Corrosion.
EC Directive 92/69/EEC B.5 Acute Toxicity (Eye Irritation).
US EPA OPPTS Guideline 870.2400 Acute Eye Irritation

- Species/Strain: Rabbit/Himalayan Chbb:HM
- Number of Animals: 3 male
- Observation Period: 72 hours
- Remarks – Method: No significant protocol deviations.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Conjunctiva: redness	0.3	0.3	0.3	2	24 hours	0
Conjunctiva: chemosis	0	0	0	0	0	0
Conjunctiva: discharge	0	0	0	1	1 hour	0
Corneal opacity	0	0	0	0	0	0
Iridial inflammation	0	0	0	0	0	0

*Calculated on the basis of the scores at 24, 48, and 72 hours for EACH animal.

Remarks – Results: Conjunctival discharge was observed in one animal at 1 hour after application, but this effect was reversible within 24 hours. Conjunctival redness was observed in all animals 24 hours after application. All observed effects were fully reversible at the 48-hour observation.

CONCLUSION	The notified chemical is not irritating to the eye.
TEST FACILITY	BASF (1999e)

B.5. Skin sensitisation

TEST SUBSTANCE	Notified chemical (99.7% pure)
METHOD	OECD TG 406 Skin Sensitisation EC Directive 96/54/EC B.6 Skin Sensitisation
Species/Strain	Guinea pig/Hsd Poc:DH
PRELIMINARY STUDY	Maximum Non-irritating Concentration: intradermal 5% (in olive oil) topical 50% (in olive oil)
MAIN STUDY Number of Animals	Test Group: 10 females Control Group: 10 females
INDUCTION PHASE	Induction Concentration: intradermal 5% (in olive oil or in a 1:1 mix of Freund's Complete Adjuvant/0.9% NaCl solution) topical 100% (undiluted)
Signs of Irritation	The intradermal induction caused moderate and confluent (grade 2) to intense erythema (grade 3) and swelling in all test animals. Partially open incrustation, in addition to moderate and confluent erythema (grade 2) and swelling were observed in all test animals after percutaneous induction.
CHALLENGE PHASE	Test topical application: 50% (in olive oil) Control topical application: olive oil
Remarks – Method	Olive oil was applied as an additional vehicle control challenge to both test and control animals. The test substance was applied to both test and non-induced control animals. The second control group (intended for a potential second challenge test) only received olive oil, as a second challenge using the test substance was deemed unnecessary due to the lack of ambiguity after the first challenge.

RESULTS

Group	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after:*			
		1st challenge		*2nd challenge*	
		24 h	*48 h*	*24 h*	*48 h*
Test	50% in olive oil	0/10	0/10	-	-
	Olive oil	0/10	0/10	-	-
Control	50% in olive oil	0/5	0/5	-	-
	Olive oil	0/5	0/5	0/5	0/5

Remarks – Results	No skin reactions could be observed after the challenge for either the control group or the test group after 24 and 48 hours. As no borderline results were observed after the first challenge, a second challenge was not conducted. Data provided for a historical positive control (α-hexylcinnamaldehyde) showed the appropriate positive result under equivalent test conditions.
CONCLUSION	There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.
TEST FACILITY	BASF (1999f)

B.6. Repeat dose toxicity (28 days)

TEST SUBSTANCE	Notified chemical (99.7% pure)
METHOD	OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents. EC Directive 96/54/EC B.7 Repeated Dose (28 Days) Toxicity (Oral). Japan/MHW: 28-day repeated dose toxicity in mammalian species.
Species/Strain	Rat/Wistar CrI: WI (Glx/BRL/HAN)BR
Route of Administration	Oral – diet
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week Post-exposure observation period: 14 days
Vehicle	None. The test substance was weighed and added directly to food.
Remarks – Method	The dose level was chosen based on the absence of toxicity observed in a dietary 14-day pre-test study.

RESULTS

Group	*Number and Sex of Animals*	*Dose in feed (ppm)*	*Equivalent dose (mg/kg bw/day)**		*Mortality*
			Males	*Females*	
Control	5 per sex	0	0	0	0/10
Low dose	5 per sex	600	64	66	0/10
Mid dose	5 per sex	3000	318	342	0/10
High dose	5 per sex	15000	1585	1674	0/10
Control recovery	5 per sex	0	0	0	0/10
High dose recovery	5 per sex	15000	1585	1674	0/10

* The equivalent dose was calculated as the mean daily test substance intake in mg/kg body weight over the entire study period.

Mortality and Time to Death

No mortality was observed during the treatment or recovery phases.

Clinical Observations

There were no effects, in any dose group, that were deemed to be treatment-related during the clinical observations, functional observational battery and motor activity measurements. The rearing reflex was found to be significantly decreased in males treated with 1585 mg/kg bw/day, but significantly increased in males treated with 318 mg/kg bw/day. Due to the lack of a dose-response relationship, this effect was considered to be incidental.

There were no treatment-related effects observed on food or water intake, or on body weight gain.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

At the end of the administration period, females treated with 1674 mg/kg bw/day showed a 50% increase in serum γ-glutamyltransferase activities. This effect was reversible upon cessation of treatment.

At the end of the administration period, males treated with 318 or 1585 mg/kg bw/day showed significantly increased serum sodium concentrations and all treated males showed increased potassium levels. These effects were reversible during the recovery period and therefore were not deemed to be toxicologically significant.

At the end of treatment, females treated with 1674 mg/kg bw/day showed reductions in total bilirubin serum concentration. All blood chemistry effects had recovered after the recovery period. No increases in serum levels of cyanide-insensitive palmitoyl-CoA oxidation were observed.

There were no treatment-related changes in the haematology parameters measured.

An increased number of degenerated epithelial cells were detected in the urine of male rats treated with 1585 mg/kg bw/day, which was reversible after the recovery period. No other treatment-related changes were observed in urine parameters.

Effects in Organs

A statistically significant decrease in body-weight relative heart weight (~8%) was observed in all treatment groups, although no effect was observed in absolute weight. These effects were considered to

be of no toxicological significance in the absence of any histopathological correlates.

Other effects (one unilateral ovarian cyst and two gastric ulcers) were considered to have arisen spontaneously.

Microscopic examination of liver did not show any signs of cell hypertrophy or any accumulation of liver peroxisomes.

Remarks – Results

The low (600 ppm) and mid (3000 ppm) dose treatment groups showed no substance related effects in either sex.

Doses of 15000 ppm caused changes in clinical chemistry parameters in animals of both sexes. Indications of mild renal function impairment (urinary epithelial cells, elevated serum Na^+/K^+) were observed in male rats. Female rats showed signs that may be associated with hepatic microsomal enzyme induction, characterised by stimulation of γ-glutamyltransferase synthesis and by increased excretion of bilirubin due to stimulation of phase II reactions.

CONCLUSION

The No Observed Adverse Effect Level (NOAEL) was established as 3000 ppm (318 mg/kg bw/day (males) and 342 mg/kg bw/day (females)) in this study, based on the absence of effects on clinical chemistry parameters at this intake level.

TEST FACILITY BASF (2000a)

B.7. Repeat dose toxicity (90 days)

TEST SUBSTANCE Notified chemical (99.6% pure)

METHOD OECD TG 408 Repeated Dose 90-Day Oral Toxicity Study in Rodents.
EC Directive 87/302/EEC B.26 90-day repeated oral dose using rodent species.
FDA: Redbook II - Subchronic Toxicity Tests with Rodents and Non Rodents.

Species/Strain Rats/Wistar CrlGlxBrlHan:WI
Route of Administration Oral – diet.
Exposure Information Total exposure days: 90 days
Dose regimen: 7 days per week
Post-exposure observation period: None
Vehicle None. The test substance was weighed and added directly to food.
Remarks – Method No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose in feed (ppm)*	*Equivalent dose (mg/kg bw/day)**		*Mortality*
			Males	*Females*	
Control	20 per sex	0	0	0	0/20
Low dose	20 per sex	1500	107.1	128.2	0/20
Mid dose	20 per sex	4500	325.7	389.4	0/20
High dose	20 per sex	15000	1102.9	1311.8	0/20

* The equivalent dose was calculated as the mean daily test substance intake in mg/kg bw over the study period.

Mortality and Time to Death

No mortality was observed during the study.

Clinical Observations

Clinical examinations revealed no treatment-related findings. Several incidental findings were observed (alopecia, mydriasis, aggressiveness, piloerection), but these occurred in single animals only in both control and treatment groups and were thus not considered to be toxicologically significant.

No treatment-related effects were observed on food or water consumption, or on body weight gain.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Significant increases in γ-glutamyltransferase activities (~60%) were found in the serum of the high dose female rats, and this was considered to be treatment-related.

Significant, dose-dependent increases in serum thyroid stimulating hormone (TSH) concentrations were observed in both males and females, but these increases were only statistically significant in high-dose females. This effect is considered to be treatment-related.

An increased number of degenerated transitional epithelial cells were found in the urine of mid and high dose males. Blood was also found in the urine of these animals at day 29.

Effects in Organs

The mean body weight-relative kidney weights were significantly increased in both male and female high dose animals (~8-10%), and in male mid (~7%) and low (~8%) dose animals. In almost all male animals, α2μ-microglobulin was detected in the epithelia and tubular lumen of the promixal tubules of the renal cortex. This staining was dose-dependent and severe in mid and high dose males. While histopathological correlates could not be found with increased kidney weights in females of the high dose group, a relationship to treatment cannot be excluded.

Relative testis weights were increased in all dose groups (~4-7%), but no histopathological correlates were found. The investigators cite the lack of dose response (equivalent response at all three doses) as evidence that these changes were not treatment related.

Relative liver weight weights were significantly increased in all high dose animals (~6% in males and ~13% in females), and in females of the mid dose group (~6%). Relative spleen weights were found to be significantly increased in male rats of the mid dose (~7%) and high dose (~9%) groups. No histopathological changes were found to account for these effects.

Significant increases in mean absolute and relative thyroid gland weights were observed in both males and females of all dose groups (~21% for the high dose groups). The decreases in thyroid weights were considered to be incidental. Minimal to slight hypertrophy/hyperplasia of thyroid gland follicular epithelia was observed for male and female rats in all dose groups including the control group. The incidence of this effect was clearly dose-dependent in males: control (2/20), low dose group (14/20), mid dose group (11/20), high dose group (16/20). A similar dose-dependency were observed in female rats: control (1/20), low dose (1/20), mid dose (3/20), and high dose (15/20) groups.

Remarks – Results

No treatment related adverse effects were noted for the low dose group.

Increased γ-glutamyltransferase and TSH values, increased thyroid gland weights as well as hypertrophy/hyperplasia of the follicular epithelia of the thyroid gland all suggest a common pathogenesis of an enzyme induction process (Curran and deGroot, 1991). Hepatic enzyme induction is characterized by enlargement of the liver, which is followed by increases in liver enzyme activities like γ-glutamyltransferase in the serum. Liver enzyme induction results in increased catabolism of thyroxine, which leads to increased TSH levels through a physiological feedback mechanism. Increased TSH levels result in thyroid follicular hypertrophy. Supporting this hypothesis is the lack of treatment-related effects on serum thyroid hormone (T3 or T4) levels, despite the elevation of TSH. Thus, effects on the thyroid gland were considered to not be adverse, and rather a consequence of liver enzyme induction.

The treatment-related kidney effects, observed in both male and female animals, are considered to be adverse. The accumulation of α2μ-microglobulin observed in male animals might suggest a rat-specific effect, and this effect was not observed in female animals. On the basis of kidney weight changes in both sexes and the appearance of degenerated epithelial cells in the urine of males, the kidney effects are considered to occur at doses of 325.7 mg/kg/day (males) and at 1311.8 mg/kg bw/day (females).

CONCLUSION

The No Observed Adverse Effect Level (NOAEL) was established as 107.1 mg/kg bw/day (males) and 389.4 mg/kg bw/day (females) in this study, based on kidney effects.

TEST FACILITY BASF (2002b)

B.8. Chronic toxicity/carcinogenicity

TEST SUBSTANCE	Notified chemical (99.6%)
METHOD	OECD 453 Combined Chronic Toxicity/Carcinogenicity Studies EC Directive 87/302/EEC B.33 Combined Chronic Toxicity/Carcinogenicity Test EPA OPPTS 870.4300; Combined Chronic Toxicity/Carcinogenicity Japan/MAFF: Combined Chronic Toxicity/Oncogenicity Study
Species/Strain	Rats/Wistar CrlGlxBrlHan:WI
Route of Administration	Oral – diet
Exposure Information	Total exposure: 24 months Dose regimen: 7 days per week Post-exposure observation period: None
Vehicle	None (administered in food)
Remarks – Method	10 animals per dose group of 60 animals made up a satellite group, which was sacrificed after 12 months. Clinical examinations (parameters include body weight, body weight change, food consumption and food efficiency) were conducted prior to the start of the administration period and weekly thereafter. Food consumption and body weight were determined weekly during the first 13 weeks, and at 4-week intervals thereafter. Signs of toxicity or mortality were examined at least once a day. Urinalysis, clinicochemical and hematological examinations were determined for satellite animals after 3, 6 and 12 months of the administration period.

RESULTS

Group	*Number and Sex of Animals*	*Nominal dose (mg/kg bw/day)**	*Mortality (% at 24 months)*	
			Males	*Females*
I (control)	60 per sex	0	20	32
II (low dose)	60 per sex	40	18	28
III (mid dose)	60 per sex	200	26	34
IV (high dose)	60 per sex	1000	14	24

*Dietary concentrations calculated to deliver the nominal dose rates were adjusted weekly during the first 13 weeks, and at 4-week intervals thereafter.

Mortality and Time to Death
Mortality was not adversely affected during the 24-month administration period.

Clinical Observations
No signs of toxicity were observed during clinical examinations.
The body weight and the mortality rate of the animals were not influenced by the administration of the notified chemical after 12 and 24 months. Food and water consumption were not affected by administration of the notified chemical. No treatment-related ophthalmoscopic findings were observed.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
In all treated males, mean corpuscular volume (MCV) was significantly reduced (low dose, 3.2%; mid dose, 3%; high dose, 4.9%) and mean corpuscular haemoglobin (MCH) was slightly but statistically significantly decreased in the low dose (4.4%) and high dose (4.4%) groups on day 182 (6 months). Low and high dose male rats showed decreased MCV (3.2% and 4.4%, respectively) and MCH values (5.4% and 5.4%, respectively) at 12 months. Slightly but statistically significant increased red blood cell counts was found in mid dose (4.8%) and high dose males (7.2%) after 12 months. After 12 months, high dose females exhibited higher platelet counts (28% increase).

Increased alkaline phosphatase activity in the serum of high dose male rats after 12 months was detected (33%) after notified chemical administration. This was possibly indicative of mild and adaptive impairment of liver function. γ-glutamyltransferase activity was increased substantially in high dose females by 154% on day 181, and by 1450% on day 357. Decreased total bilirubin concentrations were detected in the high dose males on days 182 (28.4%) and 359 (22%). In the high dose females, decreased bilirubin concentrations were detected on days 96 (28.3%), 181 (25.6%), and 357 (40.4%). Hepatic enzyme induction in the rat is characterised by stimulation of γ-glutamyltransferase activity in the liver and by increased excretion of bilirubin as a result of enhanced activation of "phase II" enzymes. As a consequence, treatment with the notified chemical induced an increase in γ-glutamyltransferase activities and a decrease in total serum bilirubin concentrations.

After 3 months of administration of the notified chemical, urinalysis revealed a significantly increased amount of degenerated transitional epithelial cells in the sediments of high dose males and granular and/or epithelial cell casts in the urine specimens of mid and high dose males. Since these effects were not apparent after 6 and 12 months of treatment, this finding was regarded as an adaptive change only and was temporary in nature. No relevant histopathological findings were seen in the kidneys after 12 or 24 months treatment.

Effects in Organs – General

Dose groups	*Males*			*Females*		
	Low	*Mid*	*High*	*Low*	*Mid*	*High*
Satellite groups (changes in absolute organ weights):						
Kidneys	+3.1%	+20.3%**	+14.2%**			
Liver	+5.2%	+15.9%*	+11.1%	+6.0%	+6.0%	+14.0%**
Thyroid glands				-18.5%*	-2.2%	+2.7%
Satellite groups (changes in relative organ weights):						
Kidneys	-3.8%	+8.0%*	+10.4%			
Liver				+11.5%	+11.7%**	+22.2%**
Final sacrifice groups (changes in absolute organ weights):						
Kidneys	-1.9%	+4.5%*	+3.1%*			
Liver	+0.8%	+6.7%*	+6.8%*	-1.0%	+6.7%	+13.8%**
Thyroid glands	-1.8%	+68.9%**	+52.4%**	+6.3%	+13.9%	+70.4%**
Uterus				-29.2%	-70.1%*	-77.5%**
Final sacrifice groups (changes in relative organ weights):						
Liver	-2.1%	+4.5%*	+1.3%	-2.5%	+4.9%	+14.6%**
Thyroid glands	0.0%	+71.4%*	+42.9%**	0.0%	+11.1%	+55.6%**

*p < 0.05; **p < 0.01

In the satellite groups (12 months sacrifice), the absolute kidney weight was increased in the mid and high dose male groups but not in the female treated groups. The absolute liver weight was also increased in the mid dose males and in the high dose females. The absolute thyroid gland weight was decreased in the low dose female group, but this is not considered treatment-related, as there was no dose-dependent effect.

In the final sacrifice groups (24 months), the mean absolute and relative weights of the thyroid glands were increased for the mid dose male rats and for both genders in the high dose group. The increased absolute kidney weights in the mid dose and high dose male groups were less marked than those seen at 12 months. There were increases in the absolute liver weights in the mid and high dose male groups and in the high dose females. The decreases in absolute uterus weights in the mid and high dose females are considered incidental due to the lesser number of tumours in the treated groups when compared to the control group.

In the satellite groups (12 months sacrifice), there was an increase in the relative kidney weight in the mid and high dose males but not in the female treated groups. Increased relative liver weights were observed in the mid dose and high dose females but not in the males. In the final sacrifice groups (24 months), there was an increase in the relative liver weight in the mid dose males and in the high dose female group. The relative thyroid glands weight was also increased in the mid and high dose males and in the high dose female group.

In the mid and high dose males, an increased number of animals with an enlarged thyroid were observed. In the high dose female group, the number of masses in the thyroid glands was slightly increased. There was an increased incidence of altered colloid in the thyroid gland, but only seen in females in the 12-month satellite groups.

After 24 months, the number of mid and high dose females with masses in the mammary gland was increased while the number of females with masses in the uterus was decreased in all dose groups. The lack of dose-response relationship suggests that the uterine effects were incidental and not treatment-related. In females, the number of foci in the liver was increased relative to controls, but there was no clear dose-response relationship, and this finding may have been unrelated to treatment. In males, there was a slight increase in numbers of liver foci, but only in the mid- and high-dose satellite groups (12 months).

Dose Group (24 months)	Males				Females			
	Control	Low	Mid	High	Control	Low	Mid	High
Thyroid gland								
enlarged	1	0	8	9	2	1	2	2
mass	3	1	3	2	0	1	1	4
altered colloid (12 mth)					0	5	3	8
Mammary gland mass					5	3	11	11
Uterine mass					11	5	9	3
Liver foci								
12 months	3	5	7	7				
24 months					5	10	20	11

Effects in Organs – Tumours

Dose Group (24 months)	Males				Females			
	Control	Low	Mid	High	Control	Low	Mid	High
Thyroid gland adenoma	3	5	11*	14**	1	3	3	9**
Hyperplasia, follicular cell	8	6	9	15	3	4	5	14
Mammary Gland								
adenocarcinoma					3	1	5	1
fibroadenoma					1	2	5	9**
Pancreas, adenoma islet cell	1	5	4	4	0	0	0	0

*$p < 0.05$; **$p < 0.01$

After 24 months of treatment, dose-related follicular cell hyperplasia and increased number of follicular adenomas were observed in the thyroid glands of male rats administered 200 mg/kg bw/day and in both genders administered 1000 mg/kg bw/day. These effects were clearly treatment-related and consistent with the increased thyroid gland weights in mid and high dose male groups and in the high dose female group.

There was a significant increase in the number of fibroadenomas in the mammary gland of high dose females after 24 months treatment. While the number of islet cell adenomas in the pancreas in treated males appeared to be increased, the changes were neither statistically significant nor dose-related. A further analysis (at the request of the US FDA) of the incidence of pancreatic and mammary fibroadenomas, using a different statistical approach in a Supplementary report confirmed the results of the main report. However, it was suggested that neither the pancreatic nor mammary fibroadenoma response should be attributed to treatment with the notified substance. The primary basis for discounting the toxicological significance of these tumours was that the incidence of mammary fibroadenomas in controls (2%) was low compared to historical control data (6-16.1%), the incidence in the high-dose group (18%) was only marginally higher than the historical incidence, and there was no increased incidence of malignancies (adenocarcinomas). The incidence of pancreatic islet cell adenomas was also within the historical control range (5-12%) as well as lacking a clear dose-response relationship in the current study.

Remarks – Results

The thyroid glands are clearly a target organ for the effects of the notified substance in rats. There was a dose-related increased incidence of follicular adenomas in the thyroid gland of mid and high dose male rats and high dose female rats. However, thyroid effects in rats are potentially secondary effects associated with liver enzyme induction and of limited relevance to humans. Such an indirect mechanism is plausible based on the findings of increased GGT activity and lower serum bilirubin levels in this study, and supported by further studies (see special studies below) on enzyme induction and cell proliferation.

CONCLUSION

The No Observed Adverse Effect Level (NOAEL) was established as 40 mg/kg bw/day (males) and 200 mg/kg bw/day (females) in this rat study, based on liver weight changes (both sexes) and kidney weight changes (males).

TEST FACILITY BASF (2005b), BASF (2006a)

B.9. Toxicokinetics

TEST SUBSTANCE	^{14}C-radiolabelled notified chemical (99.9%)
METHOD	OECD 417 Toxicokinetics EC Directive 87/302/EEC B.36 Toxicokinetics US EPA OPPTS 870.7485 Metabolism and Pharmacokinetics. Japan/MAFF Tests on In Vivo Fate in Animals, 2001

STUDY DESIGN AND OBJECTIVE

The study is intended to determine the absorption, distribution, elimination and biokinetics of the test substance in male and female Wistar rats after oral (gavage) and intravenous administration.

The following oral dose levels and experimental designs were used (test substance suspended in 0.5% aqueous carboxymethylcellulose and 1% Cremophor EL):

(1) Pre-test:	1000 mg/kg bw (2M and 2F)
(2) Blood/plasma levels:	50, 300 and 1000 mg/kg bw (4M and 4F per dose group)
(3) Balance/excretion:	20 and 1000 mg/kg bw (4M and 4F per dose group; also 4M and 4F for the 14-day repeat dose study)
(4) Tissue distribution:	20 and 1000 mg/kg bw (12M and 12F per dose group)
(5) Excretion via bile:	20 and 1000 mg/kg bw (4M and 4F per dose group)

The 20 mg/kg bw dose level was chosen because it was considered to be similar to the maximum of the expected human exposure range. The notified chemical was also dosed intravenously (by injection into the tail vein of 4M and 4F rats) at 3 mg/kg bw (in untreated rat plasma), for balance/excretion studies.

RESULTS

(1) Pre-test

No clinical signs were observed after a single oral dose, within a 48-hour observation period.

(2) Blood/plasma levels

Kinetic parameters were similar between the three dose levels and in both sexes. Absorption was rapid at all dose levels, with a maximal plasma concentration observed after 1-2 hours. In the mid and high-dose animals, a biphasic absorption was observed, with an initial peak occurring at 1 hour and a second at 4-8 hours after dosing. Thereafter, plasma concentrations declined rapidly and biphasically with half-lives of 4.4-11.9 hours.

An evaluation of AUC values (µg Eq.hour/g) showed that the total of absorption processes were saturated with increasing doses over the entire dose range investigated (e.g. increasing the dose from 300 to 1000 mg/kg bw only resulted in a 1.25-fold increase in AUC values, c.f. a >3-fold increase in dose).

(3) Balance/excretion

After a single oral dose of 20 mg/kg bw, mean total recoveries of radioactivity of 93.1% in males and 92.60% in females. Within 168 hours after administration about 30% (males) and 32% (females) of the administered radioactivity were excreted in urine. After 168 hours the total amount of radioactivity excreted via faeces was approximately 63% for males and 59% for females.

After a single oral dose of 1000 mg/kg bw, mean total recoveries of radioactivity were 92.01% in male rats and 99.42% in female rats. Within 168 hours after administration, 86.41% (males) and 93.55% (females) of the administered radioactivity were excreted via faeces. After 168 hours the total amount of radioactivity excreted in urine was found to be 5.37% for males and 5.30% for females.

No radioactivity was detected in exhaled air following any dose.

After repeated oral administration of the high dose (fourteen doses of 1000 mg/kg bw/day non-radiolabelled test substance followed by one dose of 1000 mg/kg bw radiolabelled test substance), the excretion pattern in both sexes was virtually identical to those after a single oral administration of 1000 mg/kg bw. This indicates that pre-treatment neither changed the excretion pattern nor time-course of excretion, and gives no indication that enzyme induction occurred.

After a single intravenous dosing of the radiolabelled test substance (3 mg/kg bw), mean total recoveries were 95.25% (males) and 93.12% (females). Within 168 hours, 43.45% (males) and 44.80% (females) of the total dose was found in urine, and 48.06% (males) and 42.95% (females) was found in faeces. These findings indicated that the test substance was excreted approximately equally into urine and bile.

The results of the balance and excretion experiments show that there was no gender difference with respect to the excretion pattern at both dose levels. The time course of radioactivity found in urine and faeces indicates rapid excretion and confirms the results from plasma kinetics studies. Saturation of gastrointestinal absorption is indicated by the lower proportion of radioactivity excreted in the urine at the high dose (~5%) compared to the low dose (~30%) level.

(4) Tissue distribution
Tissue distribution radioactivity measurements were performed at 1, 8, 21 and 28 hours after oral administration of 1000 mg/kg bw, and at 1, 4, 9 and 16 hours after oral administration of 20 mg/kg bw. Generally, tissue radioactivity levels for both sexes were comparable at the respective time points and dose levels, and tissue concentrations declined similarly at both dose levels. The highest radioactivity was found in the gastrointestinal tract, adrenal glands, and liver; the lowest was found in brain, muscle, and bone.

For both dose groups and both sexes, the tissue concentrations of radioactive substance declined rapidly after reaching the peak serum concentration (1-8 hours post-dosing). Initial half-lives of radioactivity concentrations in plasma, kidney and liver were calculated to be 3-10 hours (in both male and female rats) with terminal half-lives of 32-74 hours. Initial half-lives of 7-20 hours were calculated for adipose tissue. Overall, the half-lives do not indicate a potential for accumulation of the test substance.

(5) Excretion via bile
Excretion via bile was determined by bile duct cannulation. Within 48 hours of administration, excretion of the test substance in bile was ~0.5% of the high dose (both sexes) and 5.93% (males) and 12.60% (females) of the low dose. There is indication that the saturation of biliary excretion occurs with increasing dose levels.

CONCLUSION
After rapid but incomplete absorption, the notified chemical distributes to all organs and tissues, with rapid excretion mainly via the faeces. The oral bioavailability of the notified chemical was calculated to be ~5-6% (high dose) and ~40-49% (low dose), based on the total excreted radioactivity. Saturation of gastrointestinal absorption was observed with increasing doses. The notified chemical showed little potential to accumulate in rats.

TEST FACILITY BASF (2003c), BASF (2005c)

B.10. Metabolism

TEST SUBSTANCE ^{14}C-radiolabelled notified chemical (>99% pure)

METHOD OECD 417 Toxicokinetics
EC Directive 87/302/EEC B. Toxicokinetics
US EPA OPPTS 870.7485: Metabolism and Pharmacokinetics
Japan/MAFF: Metabolism Animals

STUDY DESIGN AND OBJECTIVE
The objective of the study was to investigate the nature of the biotransformation products of a ring-radiolabelled test substance in excreta and bile of Wistar rats. The test substance was administered orally (suspended in 0.5% aqueous carboxymethylcellulose with 1% Cremophor EL), or intravenously (suspended in plasma of untreated rats).

The following doses and experimental design was used:

(1) *Metabolite pattern in urine and faeces extracts:* single oral dose of 20 or 1000 mg/kg bw (4M and 4F per dose group); repeated 1000 mg/kg bw/day for 14 days (4M, 4F); intravenous 3 mg/kg bw (4M, 4F).

(2) *Metabolite pattern in bile:* single oral dose of 20 or1000 mg/kg bw (4M and 4F per dose group).

Metabolite patterns were determined by radio-HPLC after oral dosing at 12-24 hours (urine and faeces) and at 0-12 hours (bile), and after intravenous administration at 0-48 hours (urine) and of 12-48 hours (faeces).

Metabolites were isolated from bile and purified for LC-MS/MS and NMR analysis. In the case of urine and faeces, the unfractionated sample (urine) or sample extract (faeces) was analysed by LC-MS/MS instead of isolating individual metabolites.

RESULTS

Metabolite pattern in urine

The radioactivity detected in urine represented between 0.6% and 4.0% of an orally administered dose. One predominant metabolite, cyclohexanedicarboxylic acid (51-75% of radioactivity present in urine) was identified in the urine of animals after single or repeated oral treatment. Two to five minor metabolites were also detected, although none exceeded 1% of the dose in the investigated fractions. These were tentatively identified as sulfate-conjugated oxidative metabolites of the cyclohexanedicarboxylic acid monoester.

After intravenous administration, the urinary metabolite patterns were very similar to those following an oral dose, with the cyclohexane dicarboxylic acid accounting for 16-17% of the dose (between 0-24 hours). The detected minor metabolites were qualitatively similar to those detected after oral administration.

Metabolite pattern in faeces

The unabsorbed, unchanged test substance accounted for 84-100% of the radioactivity in faeces extracts after oral administration (24-76% of the administered radioactive dose at the investigated time points), reflecting its low oral bioavailability. A small amount of cyclohexane dicarboxylic acid monoisononyl ester was detected in the faeces extracts of low dose animals.

Metabolite patterns in faeces after intravenous administration were different compared to those after oral administration. No unmetabolised test substance was detected, although numerous metabolites were detected. These included cyclohexanedicarboxylic acid monoisononyl ester, which accounted for approximately 3% of the administered dose over 12-48 hours. The residual metabolites were characterised as comprising oxidation/hydroxylation products of the monoester.

Metabolite pattern in bile

The LC-MS/MS data of bile identified two to four groups of peaks. The most prominent metabolite was identified as the glucuronic acid conjugate of the monoisononyl ester, which represented 54-65% of the radioactivity in the bile (3.75/7.60% of the dose for females/males). Small amounts of the monoisononyl ester were also detected. The third metabolic fraction was characterised to contain degradation products of the monoisononyl ester (with or without further conjugation) and other derivatives/conjugates that may lack both isononyl groups.

CONCLUSION

A metabolic pathway of the notified chemical was independent of the dose level or of the sex of test animals:

(1) Partial hydrolysis of the diisononyl ester of cyclohexane dicarboxylic acid to yield the monoisononyl ester;
(2) Two further metabolic transformations of the monoisononyl ester were observed:
    i. its direct glucuronidation along with oxidation/hydroxylation and subsequent conjugation;
    ii. the hydrolysis of the remaining ester bond to yield free cyclohexanedicarboxylic acid (which accounts for the acid being the predominant metabolite in urine).

After intravenous administration of the notified chemical, the same metabolic transformations were observed, although its metabolism to polar metabolites was efficient and complete – no unmetabolised diisononyl ester of cyclohexane dicarboxylic acid was detected in urine or faeces.

TEST FACILITY	BASF (2005d)

B.11. Liver enzyme induction study

TEST SUBSTANCE	Notified chemical (99.7% pure)	
METHOD	2-week Liver enzyme induction study (no official test guideline available) OECD GLP Principles used	
Species/strain	Rat/Wistar CrlGlxBrlHan:WI	
Route of administration	Oral - diet	
Exposure information	Total exposure days:	2 weeks
	Dose regimen:	7 days per week
Vehicle	None. The test substance was weighed and added directly to food.	
Remarks - Method	The notified chemical was administered to Wistar rats (5/sex) at a dietary concentration of 15000 ppm over 2 weeks to determine the potential of the test substance to induce hepatic liver enzymes. This dose level was ~50% higher	

than the high dose administered in the 2-year chronic toxicity/carcinogenicity rat study.

Equivalent doses: males (1,418 mg/kg bw/day), females (1,568 mg/kg bw/day).

Upon completion of the study, the following parameters indicative of liver enzyme induction were examined:

- Cytochrome P450 (Cyt.P450)
- Ethoxyresorufin O-deethylase (EROD)
- Pentoxyresorufin O-depentylase (PROD)
- Benzoxyresorufin O-debenzylase (BROD)
- 4-Methylumbelliferone glucuronyltransferase (MUF-GT)
- 4-Hydroxybiphenyl glucuronyltransferase (HOBI-GT)

RESULTS

The treated rats showed a significant increase in liver Cyt.P450 activity in both male and female rats (2.2 fold for both sexes). Male and female rats also showed significant increases in the activities of liver EROD (2.7 and 1.6 fold, respectively), PROD (30 and 43 fold, respectively), BROD (11 and 24 fold, respectively), MUF-GT (3.3 and 2.4 fold, respectively), and HOBI-GT (7.2 and 2.7 fold, respectively).

CONCLUSION

The notified chemical is an inducer of both phase I (oxidative) and phase II (glucuronyl transferase) metabolic pathways in livers of both male and female rats.

TEST FACILITY BASF (2005e)

B.12. Cell proliferation study

TEST SUBSTANCE	Notified chemical (99.6% pure)
METHOD	S-phase cell proliferation study (no official test guidelines available) OECD GLP Principles used
Species/strain	Rat/Wistar CrlGlxBrlHan:WI
Route of administration	Oral - diet
Exposure information	Total exposure duration: 1, 4 and 13 weeks Dose regimen: 7 days per week
Vehicle	None. The test substance was weighed and added directly to food.
Remarks - Method	This study was conducted to determine the effects of the notified chemical on S-phase cell proliferation in critical toxicity target organs in Wistar rats after administration in the diet for 1, 4 and 13 weeks. Cell proliferation (S-phase response) was assessed in liver, kidneys and thyroid glands using BrdU (5'-bromo-2-deoxyuridine), administered one week prior to necropsy using subcutaneously implanted osmotic minipumps.

Group	*Dose level (mg/kg bw/day)**		*Treatment duration (weeks)*	*Number and Sex of Animals*
	Males	*Females*		
Control	0	0	1	10 per sex
			13	10 per sex
Low dose	40	40	1	10 per sex
			4	10 per sex
			13	10 per sex
Mid dose	200	200	1	10 per sex
			4	10 per sex
			13	10 per sex
High dose	1000	1000	1	10 per sex
			4	10 per sex
			13	10 per sex

*The concentration (ppm) of the notified chemical in food was adjusted weekly by body weight and food intake.

RESULTS

Induction of cell proliferation was found in all three organs examined (liver, thyroid glands and kidneys).

Highest levels of proliferation were found after 1 week of treatment, but were less pronounced after 4 weeks, and approached control levels after 13 weeks of treatment. While increased cell proliferation was observed at all dose levels, the pattern of response was both organ- and sex-dependent.

Liver weight increases were observed in high dose males at 4 weeks, and at all dose levels in females at week 4 but only in the high dose group at week 1. There were no changes in absolute or relative weights for kidneys or thyroid glands, although data for thyroid glands for the mid dose and high dose males and high dose females was missing due to technical issues. An increase in liver cell proliferation was observed in male rats after 4 weeks for the low and high dose groups and after 1 week for the high dose group.

There was no cell proliferation observed in the kidneys of females at any dose or time period. In males, significant proliferation was observed in the mid and high dose groups at 1 and 4 weeks but not at week 13. These effects were primarily seen in the cortex. At 13 weeks, the only significant increased labelling was seen in the outer stripe of the medulla but only in the low dose group. The lack of a clear dose-response relationship for the 13-week kidney findings suggests that their toxicological significance is questionable.

A significant increase in cell proliferation in the thyroid glands, as measured by BrdU staining, was observed at all dose levels in both male and female rats at 1 and 4 weeks but not at week 13. The incidence of follicular cell hypertrophy was both dose- and time-dependent, as shown in the table below:

		Dose groups (mg/kg bw/day)							
Observation	*Week*	*Males*				*Females*			
		Control	*40*	*200*	*1000*	*Control*	*40*	*200*	*1000*
Follicular hypertrophy	1	2	2	2	7	0	1	3	5
	4	2	2	2	8	0	0	2	3
	13	1	3	10	9	0	0	0	10
Altered colloid	13	0	1	4	6	0	0	0	2

*10 rats examined per group (only 8 for 4-week male controls).

CONCLUSION

Cell proliferation induced by the notified chemical was observed in the liver and thyroid glands, and to a lesser extent in kidneys (males only). Liver and thyroid cell proliferative effects were apparent in all dose groups of both sexes, but mainly after 1 and 4 weeks of treatment. By week 13, the cell proliferation response had subsided. However, there was evidence of follicular cell hypertrophy, mainly in the mid and high dose groups of both sexes, which progressively increased towards 13 weeks of treatment.

TEST FACILITY BASF (2005f)

B.13. Thyroid function study

TEST SUBSTANCE Notified chemical (99.7%)

METHOD Thyroid function study in male Wistar rats using perchlorate discharge as a diagnostic test (no official test guideline available). OECD GLP principles used.

Species/strain Rat/Wistar CrlHan:WI
Number/sex of animals 6 males per group
Route of administration Oral – diet
Exposure information Dose: 15000 ppm (equivalent to 1301 mg/kg bw/day)
Total exposure days: 4 weeks
Dose regimen: 7 days per week
Vehicle None. The test substance was weighed and added directly to food.
Remarks - Method The aim of the present study was to use the perchlorate discharge assay (PDA) to investigate if the effects of the test substance on the thyroid gland in male Wistar rats occur via a direct effect inhibiting the iodination in the thyroid gland or by indirect mechanisms (i.e. the liver).

The effects of the notified chemical were compared to a direct-acting chemical, propylthiouracil (PTU; 2000 ppm in the diet), which directly effects thyroid function by blocking iodide incorporation, and an indirectly-acting chemical, phenobarbital (PB; 1000 ppm in the diet), which increases TSH levels via enhanced T4 clearance from induction of liver glucuronyltranferase activity.

T3, T4 and TSH concentrations were determined from blood samples on day 27. After 4 weeks (day 29), the animals received 0.5 mL of radiolabelled NaI (^{125}iodide) by intraperitoneal (i.p.) injection, followed six hours later with an i.p. injection of either 0.9% saline solution or 10 mg/kg bw potassium perchlorate (3 rats per group). Rats were sacrificed 2.5 minutes after saline or perchlorate administration. Radioactivity was counted in the blood and thyroid to determine the ratio of ^{125}iodide between thyroid and blood.

RESULTS

Remarks - Results: Both phenobarbital (1000 ppm) and the notified chemical (15000 ppm) caused statistically insignificant changes in T3, T4 and TSH, a significant increase in thyroid weight and uptake of radiolabelled iodide uptake into the thyroid, and a significant increase in the ratio of ^{125}iodide measured in the thyroid versus the blood (phenobarbital: 57% and 77% with and without perchlorate treatment respectively; versus 134% and 28% for the notified chemical).

In contrast, PTU administration (2000 ppm) caused a significant decrease in T4 and T3 concentrations, a significant increase in TSH concentrations, a marked increase in thyroid weights, a significant reduction in ^{125}iodide uptake in thyroid after perchlorate administration, a discharge of ^{125}iodide after perchlorate administration, and a significant reduction (95% and 85%, with and without perchlorate) in the ratio of ^{125}iodide measured in the thyroid versus the blood.

CONCLUSION: The significant increase of ^{125}iodide uptake in the thyroid after administration of the notified chemical and the absence of radiolabelled iodide discharged after co-administration with perchlorate supports the finding that the notified chemical acts like phenobarbital, and indirectly promotes thyroid toxicity in the rat by inducing hepatic metabolic enzyme activities.

TEST FACILITY: BASF (2005g)

B.14. Mutagenicity – bacteria

TEST SUBSTANCE: Notified chemical (>99% pure)

METHOD: OECD TG 471 Bacterial Reverse Mutation Test.
EC Directive 92/69/EEC B.13/14
Pre-incubation test (test 1) and plate incorporation method (test 2).

Species/Strain: *S. typhimurium*: TA1535, TA1537, TA98, TA100.
E. coli: WP2 uvrA.

Metabolic Activation System: Aroclor 1254-induced rat liver S9 mix.

Concentration Range in Main Test:
a) With metabolic activation: 20-5000 μg/plate (test 1)
4-2,500 μg/plate (test 2)
b) Without metabolic activation: 20-5000 μg/plate (test 1)
4-2,500 μg/plate (test 2)

Vehicle: Acetone

Remarks – Method: No significant protocol deviations. No preliminary test was reported.

RESULTS

Metabolic Activation	*Test Substance Concentration (μg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Present				
Test 1	-	≥2,500	≥2,500	Negative
Test 2	-	≥2,500	≥2,500	Negative
Absent				
Test 1	-	≥2,500	≥2,500	Negative
Test 2	-	≥2,500	≥2,500	Negative

Remarks – Results | A weak bacteriotoxic effect was occasionally observed under all test conditions. The test substance did not lead to an increase in the number of revertant colonies, either with or without S9 mix.

CONCLUSION | The notified chemical was not mutagenic to bacteria under the conditions of the test.

TEST FACILITY | BASF (2000b)

B.15. Genotoxicity – *in vitro* chromosome aberration test

TEST SUBSTANCE | Notified chemical (>99% pure)

METHOD | OECD TG 473 In vitro Mammalian Cytogenetic Test.
EEC Directive 92/69/EC B.10 In Vitro Mammalian Chromosome Aberration Test

Species/Strain | Chinese hamster (source of cultured cell line)
Cell Type/Cell Line | V79 cells
Metabolic Activation System | Phenobarbital/3-naphthoflavone-induced rat liver S9 mix
Vehicle | Acetone
Remarks – Method | The final concentration of cyclophosphamide (positive control) with metabolic activation was changed to 0.7 µg/mL (2.5 µM).

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period (hours)*	*Harvest Time (hours)*
Present			
Test 1	6.3, 12.5, 25*, 50*, 100*, 200*	4	18
Test 2	50, 100*, 200*, 300, 400*	4	18
Test 3	12.5, 25*, 50*, 100*, 200*, 400	4	28
Absent			
Test 1	6.3, 12.5, 25*, 50*, 100*, 200*	4	18
Test 3A	25*, 50*, 100*, 200, 500, 1000*	18	18
Test 3B	25*, 50*, 100*, 200, 500, 1000*	18	28

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Present				
Test 1	-	>200	≥200	Negative
Test 2	-	>400	≥100	Negative
Test 3	-	≥100	≥50	Negative
Absent				
Test 1	-	>200	≥100	Negative
Test 3A	-	>1000	≥100	Negative
Test 3B	-	>1000	≥100	Negative

Remarks – Results | No statistically significant increases in structural chromosomal changes or polyploid metaphase frequencies were associated with treatment, compared with concurrent controls.

A slight increase in chromosomal aberration frequency was observed at 200 in the presence of S9 in Test 1; however, this increase was not statistically significant and was not reproducible under similar conditions in Test 2. In addition, a single statistically significant increase in chromosomal aberration rate was observed at 100 in Test 2 in the presence of S9. This increase was within the range of historical controls and was not observed at higher doses in the same study.

The positive controls produced the expected significant increases in the frequency of chromosomal aberrations, demonstrating the sensitivity of the experimental conditions employed.

CONCLUSION The notified chemical was not clastogenic to V79 cells treated *in vitro* under the conditions of the test.

TEST FACILITY RCC (2000)

B.16. Mutagenicity – *in vitro* gene mutation test

TEST SUBSTANCE Notified chemical (99.6% pure)

METHOD OECD TG 476 In vitro Mammalian Cell Gene Mutation Test.
EC Directive 2000/32/EC B.17 Mutagenicity - *In vitro* Mammalian Cell Gene Mutation Test.

Species/Strain Chinese hamster (source of cultured cell line)
Cell Type/Cell Line CHO cells (substrain K1)
Metabolic Activation System Aroclor 1254-induced rat liver S9 mix
Vehicle Acetone
Remarks – Method The dose range was selected on the basis of a pre-test for cytotoxicity, where no toxic effects were observed up to 5000 µg/mL, despite the presence of distinct test substance precipitation.

In Test 1, the S9 to cofactors ratio was 3:7 in the S9 mix, whereas in Test 2, this ratio was 1:9.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Expression Time*	*Selection Time*
Present				
Test 1	0, 312.5, 625, 1250, 2500, 5000	4 hrs	7-9 days	1 wk
Test 2	0, 312.5, 625, 1250, 2500, 5000	4 hrs	7-9 days	1 wk
Absent				
Test 1	0, 312.5, 625, 1250, 2500, 5000	4 hrs	7-9 days	1 wk
Test 2	0, 312.5, 625, 1250, 2500, 5000	4 hrs	7-9 days	1 wk

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Present	>5000			
Test 1		>5000	N.D.*	Negative
Test 2		>5000	N.D.*	Negative
Absent	>5000			
Test 1		≥1250	≥312.5	Negative
Test 2		>5000	≥312.5	Negative

*Not determined. Could not be determined due to precipitation of S9 mix in the culture medium.

Remarks – Results No changes in cell morphology (from completely attached, fibroblast-like cells) were observed during the study. While the test substance did not induce any increases in the frequency of mutant colonies in this study, precipitation of either the notified chemical or S9 mix (or both) were observed at all dose levels. Therefore, the effective concentration of test substance present in the culture medium throughout the experiment is not known, but is expected to be significantly lower than the nominal concentration. Any non-mutagenic conclusions for the notified chemical are dubious on the basis of this study alone.

The positive control substances produced the expected significant increases in the frequency of mutant colonies, demonstrating the sensitivity of the experimental conditions employed.

CONCLUSION The notified chemical was not observed to induce mutations in CHO cells treated *in vitro* under the conditions of the test.

TEST FACILITY BASF (2001b)

B.17. Genotoxicity – *in vivo*

TEST SUBSTANCE Notified chemical (99.6% pure)

METHOD OECD TG 474 Mammalian Erythrocyte Micronucleus Test.
EC Directive 2000/32/EC Annex 4C

Species/Strain Mouse/NMRI
Route of Administration Intraperitoneal injection (10 mL/kg bw)
Vehicle Olive oil
Remarks – Method This study includes an extra observation time (2-4 hours), which differs from the original protocol.

Dose (mg/kg bw)	*Number and Sex of Animals*	*Sacrifice time (hours)*
0	6 males	24
0	6 males	48
500	6 males	24
1000	6 males	24
2000	6 males	24
2000	6 males	48
40 (CP)	6 males	24

CP=cyclophosphamide (positive control).

RESULTS

Doses Producing Toxicity All animals in the highest dose group (2000 mg/kg bw) showed evidence of toxicity (reduction in spontaneous activity, apathy) up to 24 hours after treatment with the test substance.

Genotoxic Effects No increase in micronucleated PCEs was observed in the bone marrow of treated animals. The positive control showed a substantial increase in the frequency of induced micronuclei, indicating that the test system was able to respond appropriately to this chemical.

Remarks – Results No decrease in the PCE/NCE ratio was observed at the maximum dose recommended by the test guideline, suggesting the absence of cytotoxic effects on the bone marrow. However, the notified chemical is expected to distribute to the bone marrow under the conditions of the test.

CONCLUSION The notified chemical was not found to be clastogenic or aneuploidogenic under the conditions of this *in vivo* mouse micronucleus test.

TEST FACILITY RCC (2001)

B.18. Developmental toxicity (rabbit)

TEST SUBSTANCE Notified chemical (99.6% pure)

METHOD OECD 414 Prenatal Developmental Toxicity Study
EC Directive 87/302/EEC B. Teratogenicity Test – Rodent And Non-Rodent

Species/Strain Rabbit/Himalayan Chbb:HM
Route of Administration Oral – diet.
Exposure Information Exposure period: day 6 – day 29 post insemination (p.i.)
Dose regimen: daily
Vehicle None (administered undiluted).

Remarks – Method	No significant protocol deviations. Implantation sites were observed at necropsy in 19-24 rabbits/group, and therefore a sufficient number of females for the purpose of the study were available.

RESULTS

Group	*Number of Animals*	*Dose (mg/kg bw/day)*		*Mortality*
		Nominal	*Actual (mean)*	
Control	25 females	0	0	0/25
Low dose	25 females	100	102.2	0/25
Mid dose	25 females	300	310.7	0/25
High dose	25 females	1000	1028.5	0/25

Mortality and Time to Death
There were no substance related mortalities in any of the dose groups. One low dose animal died on day 26 p.i. There were no findings at necropsy to explain the sudden death.

Effects on Dams
There were no substance-related effects on the does regarding food consumption, body weight, body weight change, uterine weights, corrected body weight change or clinical and necropsy observations up to and including a dose of 1000 mg/kg body weight/day.

There were no significant toxicological differences between the controls and the substance treated groups on the gestational parameters (i.e. conception rate, mean number of corpora lutea, total implantations, resorptions and live foetuses and foetal sex ratios) or in the values calculated for the pre- and post-implementation losses.

Effects on Foetus
There were no substance-related differences reported for the placental and foetal body weights. The external, soft tissue and skeletal examinations of the foetuses revealed no toxicologically relevant differences between the control and the substance treated groups.

Remarks – Results
Under the conditions of this study, the test substance elicited no signs of maternal toxicity, had no influence on gestational parameters and induced no signs of developmental toxicity up to 1000 mg/kg bw/day administered to pregnant Himalayan rabbits.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) was established to be 1000 mg/kg bw/day in this study, based on maternal and prenatal developmental toxicity.

TEST FACILITY BASF (2004b)

B.19. Developmental toxicity (rat)

TEST SUBSTANCE	Notified chemical (99.7% pure)
METHOD	OECD 414 Prenatal Developmental Toxicity Study EC Directive 87/302/EEC B. Teratogenicity Study – Rodent And Non-Rodent EPA OPPTS 870.3700: Prenatal Developmental Toxicity Study
Species/Strain	Rat/Wistar CrlGlxBrlHan:WI
Route of Administration	Oral – gavage.
Exposure Information	Exposure period: day 6 – day 19 post coitum Dose regimen: daily
Vehicle	Olive oil
Remarks – Method	No significant protocol deviations. Implantation sites were found at necropsy in 21-24 rabbits/group; therefore, a sufficient number of females for the purpose of the study were available.

RESULTS

Group	Number of Animals	Dose (mg/kg bw/day)	Mortality
Control	25 females	0	0/25
Low dose	25 females	200	0/25
Mid dose	25 females	600	0/25
High dose	25 females	1200	0/25

Mortality and Time to Death
There were no substance-related or spontaneous mortalities in all of the groups at all dose levels.

Effects on Dams
There were no substance-related effects on the dams concerning food consumption, body weight, body weight change, uterine weights, corrected body weight change, clinical and necropsy observations up to and including a dose of 1200 mg/kg body weight/day.

There were no significant toxicological differences between the controls and the substance treated groups on the gestational parameters (i.e. conception rate, mean number of corpora lutea, total implantations, resorptions and live foetuses and foetal sex ratios) or in the values calculated for the pre- and post-implementation losses.

Effects on Foetus
There were no substance-related differences reported for the placental and foetal body weights. The external, soft tissue and skeletal examinations of the foetuses revealed no toxicologically relevant differences between the control and the substance treated groups.

Remarks – Results
Under the conditions of this study, the test substance elicited no signs of maternal toxicity, had no influence on gestational parameters and induced no signs of developmental toxicity up to and including a dose of 1200 mg/kg bw/day administered to pregnant rats.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) was established to be 1200 mg/kg bw/day in this study based on maternal and prenatal developmental toxicity. This is above the limit dose of 1000 mg/kg bw/day.

TEST FACILITY BASF (2002c)

B.20. Pre-/postnatal developmental toxicity study

TEST SUBSTANCE Notified chemical (99.7% pure)

METHOD The method was based on the publication of Mylchreest *et al* (1998), with elements of the following Guidelines:
OECD 414 Prenatal Developmental Toxicity Study
OECD TG 415 One-Generation Reproduction Toxicity Study
EC Directive 87/302/EEC B. Teratogenicity Study
EC Directive 87/302/EEC B. One-Generation Reproduction Toxicity Test
EPA OPPTS 870.3800: Reproduction and Fertility Effects
EPA OPPTS 870.3700: Prenatal Developmental Toxicity Study

Species/Strain Rats/Wistar CrlGlxBrlHan:WI
Route of Administration Oral – gavage.
Exposure Information Only F0 generation females
Exposure period: day 6 – day 20 post partum
Dose regimen: daily
Vehicle Olive oil
Remarks – Method The F0 females were allowed to litter and rear their pups until day 21 after parturition. At this time all male pups and up to 3 female pups per litter were selected and raised until days 100 to 105 post partum (with no additional exposure) and particularly examined for their sexual maturation (testes descending, day of vaginal opening/balanopreputial separation).

Anogenital distance measurements were performed on all live F1 pups on day 1 after birth and the anogenital index (anogenital distance/pup weight) was calculated for all pups. Further more, all surviving male pups were checked for the presence of signs of areolae/nipples from day 12 until day 15 post partum.

The dose groups (10 females) were smaller than is recommended in the OECD Guidelines (20 females), but the same as those used by Mylchreest *et al* (1998).

RESULTS

Group	*Number of Animals*	*Dose (mg/kg bw/day)*	*Mortality*
Control	10 females	0	0/10
. Low dose	10 females	750	0/10
High dose	10 females	1000	0/10

Mortality and Time to Death
There were no substance-related mortalities in any of the parental female rats in all of the doses tested.

Effects on Dams
The parental female rats showed no substance-related changes to food consumption during gestation and lactation. No test substance-related effects in organ weights, gross findings, reproductive performance and clinical examinations were observed for the parental female rats of both the 750 and 1000 mg/kg bw/day dose groups. Gestation, parturition and lactation of the parental female rats were unaffected by the administration of the test substance.

Effects on 1st Filial Generation (F1)
Clinical examinations, sexual maturation, organ weights, gross and histopathological findings and sperm motility all showed no indications of substance-related adverse effects.

There was a marginal (about 7-8% lower than the respective control values), but statistically significant decrease of the anogenital distance (AGD) in the high dose males and of the anogenital index (AGI) in high dose males and females. These were considered to be spurious, with no biological relevance because:

- all other corresponding sexual developmental parameters did not show any substance-related adverse effects;
- the female AGI was lowered to the same extent as the male AGI, which is contradictory for the reduction in AGI being an indicator of an impaired androgen-mediated development of the male reproductive tract; and
- the variability in the open literature (Clark, 1998) were considered to be similar to those seen in the present study.

In addition, any effects on sexual development/reproductive performance were investigated in the follow-up full-scale two-generation study (see below).

Remarks – Results
The findings of this pre-/postnatal developmental toxicity study of the notified chemical shows no indications that the test substance induced any adverse effects in the parental female rats. There were no indications of any developmental toxicity in the F1 pups in terms of data obtained during gestation and lactation. No substance-related clinical and pathological observations were made for the F1 progeny. The administration of the test substance to the parental female rats showed no influence on sexual organ morphology and sexual maturation of the selected F1 rats of both genders, or on sperm motility of the males.

CONCLUSION
Based on the conditions of this study, the No Observed Adverse Effect Level (NOAEL) for reproductive performance and systemic toxicity of the parental female rats is 1000 mg/kg bw/day.

The NOAEL for developmental toxicity (based on the growth and development of the offspring, including sexual organ morphology and sexual maturation) is also 1000 mg/kg bw/day for F1 progeny.

TEST FACILITY BASF (2002d)

B.21. Toxicity to reproduction – two generation study

TEST SUBSTANCE	Notified chemical (99.6% pure)
METHOD	OECD 416 Two-Generation Reproduction Toxicity Study EC Directive 87/302/EEC B35. Two-Generation Reproduction Toxicity Test EPA OPPTS 870.3800: Reproduction and Fertility Effects
Species/Strain	Rats/Wistar CrlGlxBrlHan:WI
Route of Administration	Oral – diet.
Exposure Information	Exposure period - female: Continuous until time of sacrifice Exposure period - male: Continuous until time of sacrifice Dose regimen: 7 days per week.
Vehicle	None (administered undiluted)
Remarks – Method	A technical error was found to have caused false positive vaginal smears for sperm in the F0 generation, which resulted in a high incidence of supposed male infertility of treated animals. This technical error related to contamination with rat sperm of the physiological saline solution used to prepare the vaginal smears. Therefore a second litter (i.e. F1B) was generated from the F0 generation.

Study design:

Weeks of study	*F0*	*F1*	*F2*
1-10	Exposure of F0 animals prior to first mating		
11-12	Mating period for F1A litters		
14-15		F1A born and litters culled on day 4 p.p. to 8 pups each	
17-18		F1A litters weaned day 21 p.p.; 25 of each sex selected for F1 parental generation; remaining pups sacrificed	
19-20	Mating period for F1B litters	Exposure of F1A animals prior to mating	
28-30	Necropsy of F0 adults (after birth and weaning of F1B litters)	Mating period for F2 litters	
31-32			F2 born and litters culled on day 4 p.p. to 8 pups each
34-35			F2 litters weaned day 21 p.p.; Necropsy of litters
36-37		Necropsy of F1 adults	

Dose groups

Generation	*Group*	*Number and Sex of Animals*	*Dose (mg/kg bw/day)*	
			Nominal	*Actual**
F0	control	25 per sex	0	0
	low dose	25 per sex	100	99-109
	mid dose	25 per sex	300	283-334
	high dose	25 per sex	1000	968-1101
F1	control	25 per sex	0	0
	low dose	25 per sex	100	94-101
	mid dose	25 per sex	300	271-301
	high dose	25 per sex	1000	942-1037

* Range of mean test substance intakes, which for females varied according to the test period (i.e. pre-mating, gestation, lactation)

RESULTS

Mortality and Time to Death

There were no substance-related mortalities in any of the male and female parental (F0) and F1 animals in any of the groups.

Effects on Parental (F0) animals:

The administration of the test substance at the dosed concentrations did not adversely affect the reproduction and delivery data of the F0 generation female animals.

The 1000 and 300 mg/kg bw/day F0 generation females showed increases in serum γ-glutamyltransferase activity, decreases in total bilirubin level. Increases in the absolute and relative liver and kidney weights of both genders were observed for the high and mid dose levels.

Effects on 1st Filial Generation (F1)

No substance-related differences occurred between the control and dose groups concerning viability and mortality of the F1 pups.

The relative and/or absolute liver and kidney weights of the F1 parental rats were significantly increased for all dose groups. F1 generation females treated with 1000 and 300 mg/kg bw/day showed increases in serum γ-glutamyltransferase activity and decreases in total bilirubin level. Decreased total serum bilirubin concentrations were also observed in 1000 mg/kg bw/day dose F1 males. Vacuolisation of the tubular epithelia was detected in the kidneys of all high dose males and 9/25 males in the mid dose group.

The absolute and relative thyroid weights for females were increased in the high dose group. Minimal to slight hypertrophy/hyperplasia of the follicular epithelia of the thyroid glands was recorded in 21/25 female rats of the high dose group and 10/25 female rats in the mid dose group. Also observed was minimal or slight (multi)focal accumulation of a flaky colloid within the lumen of the follicles of the thyroid glands in 12/25 female rats in the 1000 mg/kg bw/day high dose group and in 10/25 female rats in the 300 mg/kg bw/day mid dose group.

Effects on 2nd Filial Generation (F2)

No substance-related differences occurred between the control and dose groups concerning the viability and mortality of F2 pups for all dose levels.

Remarks – Results

Gross and histopathological findings did not indicate that the test substance adversely affected reproductive performance or fertility in the parental or first filial generation rats for all dose groups. There were no substance-induced signs of developmental toxicity in the progeny of F0 and F1 generation animals.

Clinical examinations for general signs of toxicity of the parental (F0) and first filial generation (F1) rats revealed no substance-induced effects for all doses of the test substance.

Clinical pathology results showing the increase in γ-glutamyltransferase activity and decreased total bilirubin levels are substance-related effects and are thought to occur as a result of the induction of the hepatic microsomal enzyme system. The increased liver weights and decreased bilirubin levels are expected to be at least partly due to this induction of hepatic microsomal enzymes. Effects due to induction of the microsomal enzyme system are interpreted as an adaptive metabolic response and are thus not considered as adverse.

Hypertrophy/hyperplasia of the follicular epithelia of the thyroid glands in the F1 generation females was considered to be a consequence of liver enzyme induction, as described in other studies, and thus is not considered to be an adverse effect of treatment.

The vacuolisation of tubular epithelia of the kidneys in the mid and high dose F1 generation males, and the observation of flaky colloid in lumen of thyroid glands follicles in the mid and high dose F1 generation females, are considered to be treatment-related.

CONCLUSION

Under the conditions of this two-generation reproduction study, the NOAEL for fertility and reproductive performance is 1000 mg/kg bw/day for F0 and F1 generation rats of both genders.

The NOAEL for general toxicity is 1000 mg/kg bw/day (F0 rats of both genders) and 100 mg/kg bw/day for the F1 male and female rats (based on tubular vacuolisation and flaky thyroid follicular colloid).

The NOAEL for developmental toxicity (growth and development of offspring) was 1000 mg/kg bw/day for the F1 and F2 pups.

TEST FACILITY BASF (2003a)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE — Notified chemical (test concentration 27 mg/L)

METHOD — OECD TG 301 B Ready Biodegradability: CO2 Evolution Test.
EC Directive 92/69/EEC C.4-C Biodegradation: Determination of the "Ready" Biodegradability: Carbon Dioxide Test
International Standard ISO 9439:1999 – Water Quality.

Inoculum — Activated sludge from laboratory wastewater plants treating municipal sewage. Concentration of dry substance was 30 mg/L.

Exposure Period — 28 days

Auxiliary Solvent — None

Analytical Monitoring — CO_2 generation

Remarks - Method — Since the test substance is not sufficiently soluble in water, no DOC degradation was determined. The test was extended to 60 days to show continuing degradation over time.

RESULTS

Test substance		*Aniline*	
Day	*% Degradation*	*Day*	*% Degradation*
7	4	14	73
14	10		
21	27		
28	41		
38	64		
49	76		
60	93		

Remarks - Results — The test substance is not readily biodegradable as the degradation of the test substance was below 60% at 28 days.

CONCLUSION — The notified chemical cannot be classed as readily biodegradable.

TEST FACILITY — BASF (2000c)

C.1.2. Bioaccumulation

TEST SUBSTANCE — Notified chemical

METHOD — OECD TG 305 Bioconcentration: Flow-through Fish Test (adapted June 1996).
US EPA, OPPTS 850.1730 Fish BCF

Species — Zebra fish (*Brachydanio rerio*)

Exposure Period — Exposure: 14 days Depuration: 16 days

Auxiliary Solvent — Acetone

Concentration Range — Nominal: 0.04 µg/L (low) 0.4 µg/L (high)
Actual: 0.041 µg/L (low) 0.41 µg/L (high)

Analytical Monitoring — Liquid scintillation counter

Remarks - Method — The control group was set up as a solvent (acetone) control. ^{14}C-radiolabelled test substance was used.

Fish samples were taken together with samples on 6 and 5 occasions during the uptake and depuration phase respectively and were analysed for the content of the test substance by measuring the total radioactivity in fish.

No toxicity in fish was expected to the solubility limit of the test substance in water (<0.05 mg/L).

RESULTS

Bioconcentration Factor	189.3 based on the mean BCFss(184.9) and BCF_k (193.7).
DT_{50}	0.5 days (low concentration), 0.6 days (high concentration)
Remarks - Results	The BCF is reported for the whole organism.

The lipid content was in a range between 2.3% and 3.6% over the entire uptake and elimination period.

The fish in the concentration groups showed no change in appearance and behaviour in comparison with the control group. No mortality was observed over the total exposure and depuration period for all test groups.

Steady state was reached within 3 days for both concentrations.

Approximately 90% of the steady state concentration of the test substance was excreted after 1.5 days for the low concentration and 1.6 days for the high concentration, indicating a very fast depuration from the organism. The elimination could be sufficiently described by first order kinetics. Based on kinetic rate constants the bioconcentration factor was 213.7 in the lower concentration group and 173.7 in the higher concentration group. The mean value was 193.7.

CONCLUSION — The notified chemical has a bioconcentration factor of less than 200, indicating that it is not likely to bioaccumulate.

TEST FACILITY — BASF (2006b)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE — Notified chemical .

METHOD — EC Directive 92/69/EEC C.1 Acute Toxicity for Fish – 96 hour, static.

Species	Zebra fish (*Brachydanio rerio*)
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	Approx. 250 mg $CaCO_3$/L
Analytical Monitoring	Probit analysis was used to determine the LC_{50}.
Remarks – Method	The stability of the test substance in the test water was not determined.

To prepare the test solution 1 g test substance was added to 10 L test water and the mixture was homogenised with ultra-turrax stirrer. The test solution was stirred for about 1 day before fish were placed into the aquaria to ensure that the limit of solubility was reached.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*				
Nominal	*Actual*		*1 h*	*24 h*	*48 h*	*72 h*	*96 h*
0	-	10	0	0	0	0	0
100	-	10	0	0	0	0	0

LC_{50}	>100 mg/L at 96 hours.
NOEC	100 mg/L at 96 hours.
Remarks – Results	No mortality occurred at a concentration of 100 mg/L. No abnormalities or symptoms were observed in the test fish during the test period.

Undissolved test substance in the form of droplets at the water surface was visible throughout the exposure period.

CONCLUSION — The notified chemical is not toxic up to the limit of its water solubility to Zebra fish.

TEST FACILITY — BASF (2000d)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical (suspended in water).
METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test part 1 - 48 hour, static. EC Directive 92/69/EEC C.2 Acute Toxicity for Daphnia - 48 hour, static. EPA OPPTS 850.1010 – Aquatic Invertibrate Acute Toxicity Test, Freshwater Daphnids. International Standard ISO 6341: 1989 – Water quality – Determination of the inhibition of the mobility of *Daphnia magna* STRAUS
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	2.49 mmol/L
Analytical Monitoring	Temperature was measured continuously throughout the test period, pH and oxygen were measured at the start of the test (0 hr) and at 48 hours.
Remarks - Method	A concentration control analysis was not conducted in this test. The stock of the notified chemical was made by stirring the test substance into water, then removing any undissolved test substance by centrifugation. In this way, Water Accommodated Fractions (WAF) were prepared by dilution of this eluate.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
0	-	20	0	0
100	-	20	0	0
50	-	20	0	0
25	-	20	0	0
12.5	-	20	0	0

LC_{50}	> 100 mg/L WAF at 48 hours (immobilisation)
NOEC	100 mg/L WAF at 48 hours (immobilisation)
Remarks - Results	No organism were immobilised in this test at the nominal concentration studied. There is no indication as to whether solutions remained clear or of the amount of test substance in the WAFs.
CONCLUSION	The notified chemical is not toxic to *Daphnia magna* up to the limit of its water solubility.
TEST FACILITY	BASF (1999g)

C.2.3. Chronic toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 211 *Daphnia magna*. Reproduction Test – 21 day, semi-static. EEC Guideline X1/691/86, Draft 4: Prolonged toxicity study with *Daphnia magna*: Effect on reproduction.
Species	*Daphnia magna*
Exposure Period	21 days
Auxiliary Solvent	Tween 20 (25 μg/L)
Water Hardness	2.2 – 3.2 mmol/L
Analytical Monitoring	Gas Chromatograph after extraction with hexane and evaluation by internal standard dibutylphthalate in hexane (concentration control

	analysis).
Remarks - Method	The test was performed with the inclusion of 25 μg/L Tween 20 in the stock solution. Only one concentration (0.03 mg/L) of the notified chemical was tested (limit test). Tween 20 (25 μg/L) was weighed in a glass beaker. The test substance (30 mg/L) was transferred into the beaker with the solvent. The solution was stirred for 60 minutes at 20 ± 2°C. The glass beaker was subjected to an ultra sonic bath for 10 minutes and later the solution was further stirred for 21 hours. The solution was transferred into a graduated flask, which was filled to 1L with M4 medium. 1 mL of this solution was transferred into 1000 mL M4 medium. The solution was renewed every 2-4 days.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*14 d*	*21*
0	0	10	0	0
0.03	0.021	10	0	0

NOEC	≥ 0.021 mg/L at 21 days
LOEC	> 0.021 mg/L at 21 days
LCD	≥ 0.021 mg/L at 21 days
Remarks - Results	As there were no significant differences between survival and reproduction for control and exposed daphnia, the observed adverse effect level is 0.021 mg/L – i.e. no effects are expected at the limit of solubility.

CONCLUSION	The notified chemical did not cause chronic toxicity at the highest concentration tested (limit water solubility).
TEST FACILITY	BASF (2004c)

C.2.4. Algal growth inhibition test

TEST SUBSTANCE	Notified chemical (aqueous extract)
METHOD	OECD TG 201 Alga, Growth Inhibition Test. EC Directive 92/69/EEC C.3 Algal Inhibition Test. EPA OPPTS 850.5400 – Algal Toxicity, Tiers I and II
Species	*Scenedesmus subspicatus*
Exposure Period	72 hours
Concentration Range	Nominal: 6.25, 12.5, 25, 50 and 100 mg/L
Auxiliary Solvent	None
Water Hardness	Not reported
Analytical Monitoring	None
Remarks - Method	A concentration control analysis was not conducted in this test because the detection limit of the analytical method was beyond the water-solubility of the test substance. To make up the stock solution, the test substance was stirred in demineralised water for 20 h at approximately 20 ± 2°C. Undissolved test substance was removed by centrifugation (c. 60 min at ~17700 *g*). The nominated concentration of 125 mg/L in the eluate was diluted to prepare the test solutions. The test substance has the potential to adsorb to glass. Therefore the test vessels were filled with an aqueous extract (eluate) of the test substance and stirred for 24 h at 100 rpm at room temperature. The eluate was changed once. The vessels were carefully rinsed with water before the test started.

RESULTS

Biomass		*Growth*	
E_bC_{50} mg/L at 72 h	*NOEC mg/L*	*E_rC_{50} mg/L at 72 h*	*NOEC mg/L*
> 100 mg/L WAF	≥ 100 mg/L WAF	> 100 mg/L WAF	≥ 100 mg/L WAF

Remarks - Results — No inhibition of biomass or growth rate was found. In fact in both cases these were higher than the control; this was significantly so in the case of the former.

CONCLUSION — The notified chemical is not toxic to algae, up to the limit of its water solubility.

TEST FACILITY — BASF (2000e)

C.2.5. Inhibition of microbial activity

TEST SUBSTANCE — Notified chemical

METHOD — OECD TG 209 Activated Sludge, Respiration Inhibition Test.
EC Directive 88/302/EEC C.11 Biodegradation: Activated Sludge Respiration Inhibition Test
International Standard ISO 8192-1986 Water Quality – Test for inhibition of oxygen consumption by activated sludge.

Inoculum — Activated sludge from laboratory wastewater plant treating municipal swage. Concentration of dry substance is 1 g/L.

Exposure Period — 180 mins

Concentration Range — 1000 mg/L (nominal)

Remarks – Method — 3,5-dichlorophenol was used as a reference.

RESULTS

EC_{50} — >1000 mg/L (nominal)

Remarks – Results — The oxygen concentration decreased more significantly for the test substance than for the blank controls.

The oxygen consumption rate did not differ between the test substance and the controls.

The oxygen consumption rate of the reference substance is significantly lower than both the rate of the test substance and the blank samples and the reference met the validity criteria (EC_{50} = 6.5 mg/L).

CONCLUSION — The notified chemical has low toxicity to bacteria.

TEST FACILITY — BASF (1999h)

C.2.6. Acute toxicity to the earthworm

TEST SUBSTANCE — Notified chemical

METHOD — OECD TG 207: Earthworm, acute toxicity tests.

Species — *Eisenia foetida*

Remarks - Method — The test involves keeping earthworms in samples of a precisely defined artificial soil to which a range of concentration of the test substance has been applied. These were 62.5, 125, 250, 500 and 1000 mg/kg.

RESULTS — LC_0 (14 day) >1000 mg/kg (nominal)
LC_{50} (14 day) >1000 mg/kg (nominal)
LC_{100} (14 day) >1000 mg/kg (nominal)

Remarks - Results — No negative impact on worm biomass was detected.

No other particular behavioural or morphological changes were observed

	at the end of the test.
	The determined pH value of 7.0 deviated from the aspired value of 6 ± 0.5. There was also deviation in the water constant of the dry test substrate from 2.2 g/100 g dry weight to the aspired value of < 2 g/100 g dry weight, but this had no effect on the result of this study.
	There was a deviation of the water content of the test substrate at the end if the test (36.9 g/100 g dry weight). The aspired value was 33 ± 2 g/100 g dry weight. This no effect on the outcome of this study.
CONCLUSION	The notified chemical is not toxic to earthworms.
TEST FACILITY	BASF (2001c)

C.2.7. Effect on emergence and growth of higher plants

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 208: Terrestrial plants, Growth Test International Standard ISO 11269-2:1995: Soil Quality Determination of the Effects of Pollutants on Soil Flora – Part 2: Effects of Chemicals on the Emergence and Growth of Higher plants.
Species	*Avena sativa* (oilseed rape) *Brassica napus* (oats) *Vicia sativa* (vetch)
Remarks - Method	The test involves incorporation of the notified chemical at various concentrations into soil with seeds subsequently sown. The number of seedlings that emerge is recorded. At least two weeks after 50% of the seedlings have emerged in the control, the plants arte harvested. Weight and shoot lengths recorded. The normal test concentrations used were 62.5, 125, 250, 500 and 1000 mg/kg.
RESULTS	The EC50 test results, relating to dry mass of the soil, for all three species *(Avena sativa, Brassica napus and Vicia sativa)* are as follows: EC50 (emergence rate) >1000 mg/kg (nominal) EC50 (dry matter) >1000 mg/kg (nominal) EC50 (fresh matter) >1000 mg/kg (nominal) EC50 (shoot length) >1000 mg/kg (nominal) The NOEC/LOEC tests results relating to the dry mass of the soil for all the three species (*Avena sativa, Brassica napus and Vicia sativa*) are as follows: NOEC/LOEC (emergence rate) ≥1000 mg/kg (nominal) NOEC/LOEC (dry matter) ≥1000 mg/kg (nominal) NOEC/LOEC (fresh matter) ≥1000 mg/kg (nominal) NOEC/LOEC (shoot length) ≥1000 mg/kg (nominal)
Remarks - Results	The results for *Avena sativa* were obtained after 20 Days and the tests results for *Brassica napus* and *Vicia sativa* were obtained after 21 days.
CONCLUSION	The notified chemical is not toxic to higher plants.
TEST FACILITY	BASF (2005h)

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Label

Eco-Efficiency Analysis

Hexamoll® DINCH

May 10th, 2008

Summary (1)

BASF
The Chemical Company

- This eco-efficiency analysis compares various non-phthalate plasticizers for use in PVC applications in the German market. Plasticizers that were compared included Hexamoll® DINCH (diisononylcyclohexane dicarboxylate), acetyltributyl citrate (ATBC), acetylated castor oil derivative, alkylsulphonic phenyl ester (ASE), and diethylhexylterephthalate (DEHTP).

- Hexamoll® DINCH is the most eco-efficient plasticizer, with the lowest overall environmental impact. DEHTP has a slight cost advantage, but is less eco-efficient primarily due to toxicity considerations. ATBC has an intermediate eco-efficiency. ASE results in comparable costs; however, it has a significantly lower eco-efficiency due to high material consumption, energy use and emissions during plasticizer production. Acetylated castor oil derivative has the lowest eco-efficiency, with low environmental performance at a much higher cost.

Summary (2)

BASF
The Chemical Company

- The results hold not only for balls (base case), but also for garden hoses and medicinal tubing. While these have somewhat different compositions, the eco-efficiency relationships remain essentially unchanged compared to the base case.
- The relative position of acetylated castor oil derivative would not be improved even if the R-phrase (R43) were not applicable.

Communication

- **Hexamoll® DINCH is the most eco-efficient non-phthalate plasticizer for PVC applications such as balls, garden hose and medicinal tubing.**
- **Hexamoll® DINCH and DEHTP are similarly priced, but the former offers significant toxicological advantages over the complete life cycle. Considering only the toxicological risk to the consumer, the advantage of Hexamoll® DINCH is even greater.**